Evidence of dental screening for oral foci of infection in oncology patients

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Thesis

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Contents

Chapter 1

Introduction and aim of the thesis

Introduction and aim of the thesis

Pre-treatment dental screening aims to locate and eliminate oral foci of infection in order to prevent local, loco-regional or systemic complications during and after treatment [1-3]. An oral focus of infection is defined as a pathologic process in the oral cavity that does not cause major infectious problems in healthy individuals, but may lead to severe local or systemic inflammation under certain circumstances [4,5].

Acute and chronic oral foci of infection can be distinguished:

- An oral focus of infection is considered acute when that focus showed one or more of the following clinical symptoms or those symptoms were reported by the patient to have occurred during the last 3 months: tooth related or oral mucosa related pain, percussion or palpation tenderness of oral structures, fever related to oral pathology, swelling of oral tissues and/or tooth related purulent drainage.
- An oral focus of infection is considered chronic when that focus had not exacerbated and was asymptomatic during the previous 3 months [6].

Dental screening usually involves clinical examination of the oral cavity, including oral mucosa, dentition, and periodontium, combined with radiographic imaging of the dentition and jaw bones [1]. Dental screening on oral foci of infection is done for a variety of patient groups at risk including head and neck cancer (HNC) patients subjected to radiotherapy and/or chemoradiation, hematologic patients subjected to high-dose or intensive chemotherapy, patients on intravenous bisphosphonates and patients with fever of unknown origin [7,8].

Frequently observed potential oral foci of infection include caries profunda, periodontal disease, periapical problems, (partially) impacted or partially erupted teeth not fully covered by bone or showing radiolucency, cysts, non-vital pulps and ulcerations [9-11]. However, which pathologic oral process should be considered as an oral focus of infection is dependent on the underlying medical problem. For example, patients with an oral squamous cell carcinoma treated with curative ionizing radiation therapy to the head and neck region possess a lifelong risk to develop treatment related sequelae, such as osteoradionecrosis (ORN) of the jaws [12,13]. Therefore, it is commonly accepted, although not evidence driven, that such patients have to be free of oral foci of infection 10-14 days before the onset of radiotherapy to allow possible tooth extraction wounds to heal [1,10]. On the contrary, the effects of chemotherapy on healthy oral tissues are essentially temporary and reversible. Thus, the risk of developing complications related to chronic oral foci of infection is probably not higher than in healthy subjects once patients have recovered from chemotherapy and their blood levels have normalized [9]. Removal of oral foci of infection can therefore be less aggressive in chemotherapy patients and can probably be limited to acute oral foci of infection and chronic oral foci of infection that have recently caused complaints.

Although frequently executed, dental screening on oral foci of infection is, as mentioned before, hardly evidence based [1-3,10]. Screening on oral foci of infection is mainly based on clinical experience and retrospective cohort studies. Moreover, even until today there is a great national and international variety between institutions when it comes to the groups of patients that are routinely seen for a dental screening as well as which oral foci of infection have to be considered as an oral focus of infection [3,14,15]. Not much seems to be changed over the years because of a lack of evidence due to a lack of well-designed studies.

In this thesis, two groups of patients in whom usually a dental screening is performed before onset of therapy are assessed, viz., HNC patients subjected to radiotherapy and hematology patients undergoing intensive chemotherapy or high-dose chemotherapy and ASCT, in order to gain more evidence for this screening on oral foci of infection.

Head and neck cancer

Radiotherapy to the head and neck region results in multiple acute and late side effects such as a reduced salivary flow (hyposalivation), a sensation of oral dryness (xerostomia), dental caries, fungal and bacterial infections, loss of taste, oral mucositis, trismus and skin-fibrosis [9,12,16]. The main reason for dental screening on oral foci of infection is to prevent acute and long-term oral sequelae, especially ORN. Comparison of the data on ORN reported in the literature is hard as no univocal definition of ORN is applied which may result in under- or overreporting of ORN. For example, many patients may have low-grade jaw complications, such as exposed bone, which is not univocally reported as ORN [17].

The last decade, radiation treatment of HNC has changed substantially, amongst others due to the introduction of intensity modulated radiation therapy (IMRT) and concomitant chemoradiation (CHIMRT) [18]. The exact effects of IMRT on the oral microflora, oral tissues and jaw bone are not yet clear, including its impact on what oral foci of infection have to be considered an oral focus of infection needing treatment before onset of therapy. For example, it has been shown that IMRT results in less xerostomia due to sparing of the parotid and/or submandibular glands [19-21]. But at the same time, sparing of, e.g., salivary glands may result in higher doses to the other tissues in the radiation field, such as the jaw bone [22]. Higher doses to jaw bone bear the risk of a higher risk of developing ORN. Therefore, a prospective cohort study has to be conducted to assess the effects of IMRT on post-radiation oral sequelae as well as to assess the efficacy of dental screening and elimination of oral foci of infection in IMRT-patients. Additionally, the effects of IMRT on oral microbial composition have to be assessed as a possible factor underlying certain post-radiotherapy oral sequelae.

Hematologic patients

Patients undergoing chemotherapy are prone to develop, often reversible, oral side effects, such as oral mucositis, xerostomia, taste changes, and local and systemic infections [23]. Intensive or high-dose chemotherapy given to hematologic patients could cause severe neutropenia (absolute neutrophil count <500/μL), which puts patients at high risk of infections, sepsis and septic shock [24]. Chemotherapy can also be given be given as adjuvant treatment in HNC patients, often combined with radiotherapy, but in a lower dose that does not cause neutropenia. It is in fact the neutropenia that makes the problems occurring in high-dose chemotherapy patients dissimilar from the problems occurring in irradiated patients, as high-dose chemotherapy neutropenia significantly increases the risk for infectious complications. However, once chemotherapy has ended, neutrophil counts return to normal thereby reducing the risk of developing oral complications related to oral foci of infection to that of healthy subjects. However, in hematologic patients undergoing high-dose chemotherapy and allogeneic stem cell transplant, oral complications may last longer and be of a different kind due to graft versus host disease [25]. These patients were not assessed in this thesis.

The efficacy of dental screening for oral foci of infection in intensively treated chemotherapy patients is questionable: Do acute and chronic oral foci of infection indeed have to be removed before onset of therapy or can the treatment of certain chronic oral foci of infection be postponed until after treatment?

In many institutions, like at the University Medical Center Groningen, the Netherlands, hematologic patients subjected to intensive chemotherapy or high-dose chemotherapy and ASCT are routinely screened for oral foci of infection before starting intensive treatment [26]. Acute exacerbation of oral foci of infection is presumed to result in bacterial translocation from the oral cavity to the blood. To minimize the risks of developing oral sequelae and to reduce the chance of developing neutropenic fever, oral foci of infection which are anticipated to potentially cause problems during chemotherapy are routinely eliminated. The literature suggests that acute oral foci of infection should be eliminated, but that certain types of chronic oral foci of infection can be left untreated [6,27,28]. The underlying studies had mixed patient groups and/or a small number of patients [6,28] or reported on the need for treatment of postendodontic asymptomatic periapical radiolucencies only [27]. Therefore, the hypothesis has to be tested that chronic oral foci of infection that did not cause complaints for at least the last 3 months do not have to be eliminated before chemotherapy in leukemic patients subjected to intensive chemotherapy and multiple myeloma (MM), non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma patients subjected to high-dose chemotherapy and autologous stem cell transplantation (ASCT).

Aim of the thesis

The general aim of this thesis was to assess the efficacy of pre-treatment dental screening in HNC patients subjected to radiotherapy as well as in hematology patients subjected to intensive chemotherapy or high-dose chemotherapy and ASCT regarding complications during treatment and follow-up.

Sub-goals

To systematically review the literature on the efficacy of pre-radiation dental screening in head and neck cancer patients (**Chapter 2**).
To retrospectively assess whether pre-radiation dental screening for oral foci of infection in head and neck cancer patients is effective (**Chapter 3**).
To retrospectively identify risk factors, related to the oral problems as observed prior to radiotherapy, for oral sequelae after radiotherapy (**Chapter 3**).
To assess the effects of radiation therapy in head and neck cancer patients on oral microbial composition in a prospective cohort study comparing patients who had surgery, postoperative or primary IMRT and postoperative or primary CHIMRT (**Chapter 4**).
To prospectively assess oral sequelae that may occur during follow-up in head and neck cancer patients treated with IMRT/CHIMRT (**Chapter 5**).
To prospectively assess the effect of leaving chronic oral foci untreated on infectious complications during intensive chemotherapy in a cohort of hematology patients (**Chapter 6**).

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Chapter 2

Evidence supporting pre-radiation elimination of oral foci of infection in head and neck cancer patients to prevent oral sequelae. A systematic review.

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Abstract

Background and purpose: Pre-radiation dental screening of head-neck cancer patients aims to identify and eliminate oral foci of infection to prevent post-radiation oral problems. The evidence for the efficacy of dental screening is unclear. In this systematic review, we analyzed available evidence on the efficacy of pre-radiation elimination of oral foci of infection in preventing oral sequelae.

Materials and Methods: A search was conducted (MEDLINE/EMBASE) for papers published up to May 2014. Papers on head-neck cancer patients subjected to pre-radiation dental screening, (chemo)radiation and oral follow-up were included.

Results: Of the 1770 identified papers, 20 studies fulfilled the inclusion criteria of which 17 were retrospective. A great heterogeneity in patient groups, dental screening techniques, definitions of oral foci of infection and techniques for eliminating foci was found. Most papers lacked essential details on how dental screening was performed and a clear definition of an oral focus of infection. The evidence for efficacy of elimination of oral foci of infection to prevent post-radiotherapy oral sequelae was inconclusive.

Conclusions: Consequently, the efficacy of pre-radiation elimination of oral foci of infection remains unclear. No conclusions can be drawn about a definition of an oral focus of infection and whether pre-radiation elimination of these foci should be mandatory.

We therefore suggest prospective studies with well-defined criteria for oral foci of infection, a clear description of which foci were eliminated and how, a detailed description of pre-radiation dental screening, clearly described patient and tumor characteristics, and a detailed dental history and dental status. Subsequently, oral problems that occur post-radiation should be systematically recorded.

Introduction

Radiotherapy is an effective treatment option for a wide variety of head and neck neoplasms. Unfortunately, it causes acute and long term adverse oral effects. While some adverse effects are unavoidable, others, in particular the risk of developing jaw osteoradionecrosis (ORN), are thought to be reduced by a thorough pre-radiation dental screening to detect oral foci of infection [1,2]. In this review we have operationalized the concept of oral focus of infection as a pathologic process in the oral cavity that does not cause major problems in healthy individuals, but may lead to severe local or systemic inflammation under certain circumstances [3,4]. A pre-radiation dental screening aims to locate and eliminate oral foci of infection, such as caries profunda, periodontal attachment loss, periapical problems and partially or completely impacted teeth [3-5], thus prevent radiation-related oral complications. Little evidence exists on the efficacy of elimination of oral foci of infection to prevent post-radiotherapy oral sequelae [5,6]. Nevertheless, pre-radiation dental screening of patients is daily practice in head and neck cancer centers [7,8]. Head and neck oncology patients are known to have poor dental status compared to healthy subjects [9-12]. The poorer dental status is thought to be related to the more frequent alcohol and tobacco abuse and lower dental awareness in these patients.

Prevention of jaw osteonecrosis associated with radiotherapy, known as osteoradionecrosis (ORN), a feared late complication of radiotherapy, is probably the main reason that dental teams all over the world perform a pre-radiation dental screening of patients [3]. Despite the extensive literature on this topic, the mechanisms underlying ORN are not well understood. One risk factor for ORN, identified in the systematic review by Nabil et al. [3], is post-irradiation extraction of the mandibular tooth within the radiation field. Consequently, post-irradiation extractions should be avoided as much as possible, and pre-radiation screening for oral foci of infection is necessary. Other risk factors for developing ORN are tumor characteristics [13,14], total radiation dose [14-16], bacterial infections [17,18], dental status [19], periodontitis [12], and surgical interventions [20].

In this systematic review we analyzed the available evidence for the efficacy of pre-radiation elimination of oral foci of infection in head and neck cancer patients to prevent post-radiotherapy oral sequelae. We focused specifically on the following questions: Is pre-radiation elimination of oral foci of infection in head and neck cancer patients efficient and should pre-radiation elimination of these oral foci be mandatory?

Materials and methods

Search strategy

A broad literature search was conducted in MEDLINE/PubMed and EMBASE for papers published up to May 2014 (Supplementary Table 1). No language filters were applied. Meta-analysis, systematic reviews, randomized controlled trials, clinical studies and cohort studies were considered as sources for evidence to answer the research question.

Review strategy

After the search was conducted, duplicates were removed and the remaining papers were subjected to title and abstract analysis by 2 reviewers (JMS, MAS) independently. Title and abstract were included for full text analysis if the terms 'head and neck cancer' and '(chemo)radiation' or synonyms were present, combined with mention of pre-radiation oral or dental care, oral or dental screening, or pre-radiation extraction, or oral status or synonyms. Single case reports, opinion papers, narrative or expert reviews, surveys, and letters to the editor were excluded, as were papers about pre-adult patients (<18 years), chemotherapy as a single treatment, surgery as a single treatment, effects of radiation on tooth structures, mucositis, and microbiology. The papers selected after title and abstract analysis were classified by study type.

The selected studies were included for full text analysis if head and neck cancer patients received external beam radiotherapy, a pre-radiation dental screening had been performed, criteria for oral foci were described (what was considered an oral focus) and patients were assessed for oral sequelae at least once after radiation (Supplementary Table 2). Two reviewers (JMS, MAS) independently analyzed the studies for the inclusion criteria and extracted data if the study was included, using a self-developed evaluation form (Supplementary Table 2). Disagreements about including or excluding studies or about extracted data were resolved after discussion. In case of insufficient information in the manuscripts for adequate assessment, the corresponding authors were contacted for more details.

Results

The search resulted in 1770 papers, 540 hits in PubMed and 1230 hits in EMBASE (figure 1). After removing duplicates, 1469 papers remained for title and abstract analysis. Out of the 234 papers eligible for full text analysis, 205 papers (63%) were available in full text on the internet and after contacting international library databases. Of these 205 papers, 124 papers (60%) were guidelines, protocols and descriptive papers that did not investigate or analyze effects of dental screening on prevention of oral sequelae, so they were excluded. The remaining 81 papers were subjected to full text analysis using the evaluation form (Supplementary

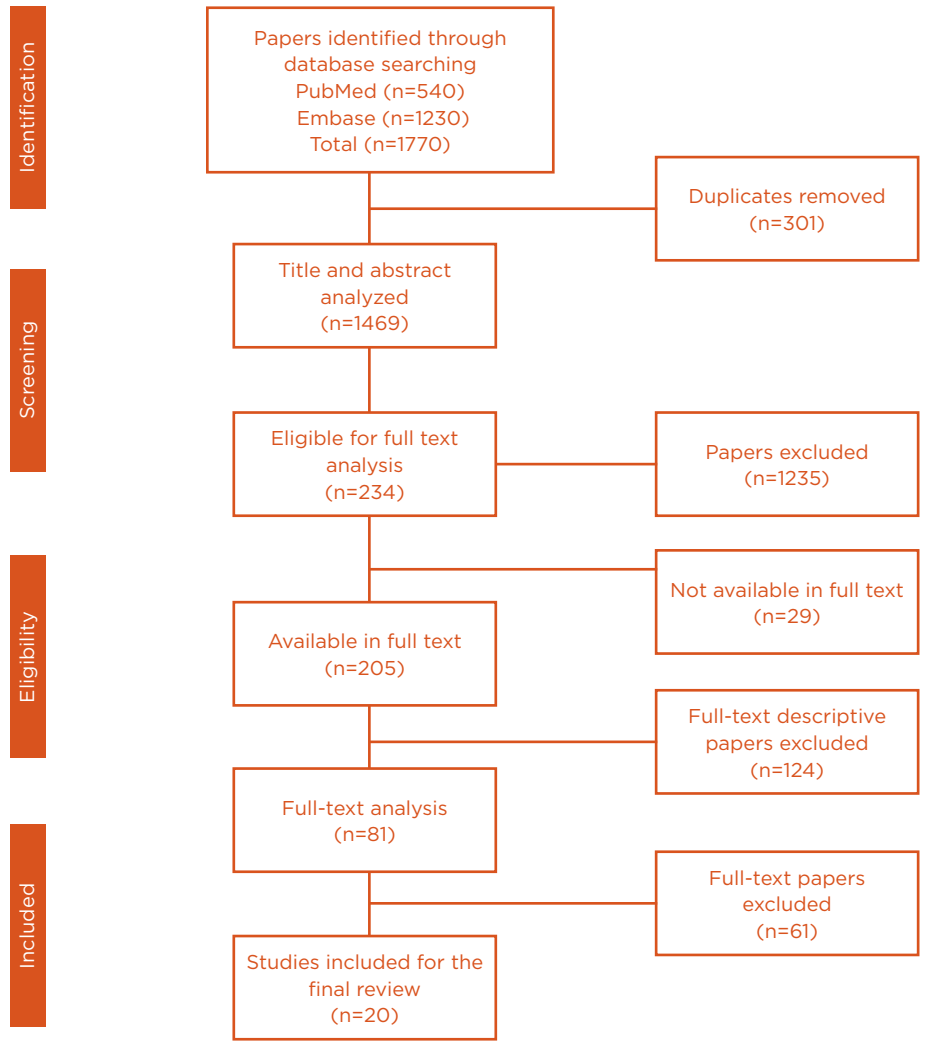

Figure 1. Flow Chart for study selection.

Table 2). No randomized controlled trials were found.

In 3 out of 81 papers, an oral focus of infection was not clearly defined. The authors of these studies were contacted for more details [9,21,22]. One author [9] did not respond and one author [21] could not provide more details. These papers were excluded. Niewald et al. [22] did provide more details on their definition of oral foci of infection.

The included papers

After full text analysis, 20 studies met the inclusion criteria (Table 1). Three papers were prospective [23-25], the others were retrospective [2,12,22,26-39]. References of the 20 included studies were checked to find any additional relevant studies. None were found.

Study characteristics

The number of patients in the included studies ranged from 28 [25] to 1140 [32] (Table 1). Duration of follow-up ranged from 6 [25,27] to 60 months [29]. Five studies did not describe the duration of follow-up [26,31,33,38,39]. Tumor location was well described in most studies (Table 1). Some studies included a great variety of tumor locations in the head and neck region. Although these were not always specified in the article, most studies included other tumor sites as well, such as unknown primary tumors, non-Hodgkin lymphoma and Hodgkin lymphoma [2,23,25,27-29,31,34,35,37,39]. Two studies [33,38] included only nasopharynx carcinoma patients. Some studies also included edentulous patients in their study population.

Pre-radiation dental screening

Most papers lacked details on how dental screening was performed (Table 2), but commonly, radiographic examination (n=14) and periodontal probing (n=19) were performed.

Oral foci of infection

The descriptions of oral foci of infection in the papers varied greatly: we found 7 definitions for periodontitis, 4 for caries, 2 for pulpal pathology and 5 for radiographic findings (Table 3). Four of the studies provided a very precise description of what was assumed to be a focus of infection, such as “caries in which excavation may lead to pulpal exposure” [12,26,34,35], but other studies lacked adequate detail in the descriptions. They used more general terms such as “active moderate periodontal disease” [37] or “advanced/severe periodontal disease” without defining the severity of periodontitis [22-24,26-32,34-38].

Nine studies reported on the findings of the dental screening [12,24,25,28,30,31, 34-36] (Table 1). In six studies [12,24,30,31,34,36] the percentage of patients presenting with oral foci was described, ranging from 20% [30] to 79% [31]. Detailed information on the type of oral foci of infection found was provided in 6 studies [12,24,25,28,34,35] (Table 1).

Generally, more recent studies reported on the presence of periodontal disease as focus of infection at pre-radiation screening, whereas in most of the older studies the periodontal condition of the patients was not reported. Prevalence of periodontitis in pre-radiation dental screening in the more recent studies ranged from 54% to 93% in dentate subjects [12,24,25].

As shown in Table 1, we found a wide variation of pre-radiation interventions to eliminate oral foci of infection, including tooth extraction (all studies), scaling and root planing (6 studies), restoration (9 studies), surgical removal of root or wisdom tooth (10 studies), endodontic treatment (4 studies), and apexification (2 studies).

Other interventions

In 16 studies, oral hygiene instructions were given before the start of radiotherapy, either as part of the dental screening or early in the treatment process [2,12,22-26,28-32,35,36,38,39]. Dental calculus removal was described as part of the dental screening or as a procedure early in the treatment process in 12 studies [12,22,24-29,31,33,36,38].

Fluoride application during and after radiotherapy was advised in 18 studies [2,12,22-30,33-39]. Most studies advised daily application of a fluoride gel. Neutral fluoride gel was prescribed in 8 studies [2,12,25,29,30,33,34,39]. The other studies did not report the type of fluoride gel [22,36] or prescribed a 1% NaF-gel [27], 2% NaF-gel or 1.23% APF-gel [38], 1.23% NaF-gel, 0.4% stannous [26,35,37] or 1.1% NaF-gel [37], NaF-gel without percentage [23] or 3% NaF-rinse [28].

Oral sequelae after radiotherapy

ORN was reported in 17 studies (Table 1). In 4 studies, ORN was defined as exposed bone through an opening in the overlying mucosa, persisting as a non-healing wound for 3 months or more [12,29,35,37]. One study used ORN of grade 2 or higher according to the classification by Glanzmann and Grätz [36]. Another study used the Common Terminology Criteria for Adverse Events version 3.0 [2]. No clear definition for ORN was found in 11 studies [22,24,26-28,30,32-34,38,39]. Prevalence of ORN ranged from 0% [2,38] to 23% [22]. In studies with a short follow-up, ORN was seldom seen [27,34]. In a study with a mean follow-up of 35 months, no cases of ORN were reported [2].

Post-radiotherapy dental extractions were reported in 13 studies [2,12,22,23,26-30,34,35,37,39]. Post-radiotherapy extractions ranged from 4% [27] to 57% of patients [34]. In 5 studies ORN was seen in patients who were subjected to post-radiotherapy extractions, but no significantly increased risk was reported for developing ORN after post-radiotherapy extractions [12,26,27,29,37]. The reason for post-radiotherapy extraction, if reported, was periodontal disease [12,28,30] or caries [30].

Evidence for effects of pre-radiation elimination of oral foci of infection in preventing oral sequelae

Prospective studies

The prospective study by Pochanugool et al. [23] analyzed the effects of three fluoride-regimes: fluoride gel, fluoride rinse or both. Patients were subjected to a pre-radiation dental screening and subsequent extraction of unrestorable teeth.

Table 1. Summary of included papers in chronological order.

Year	Author	Study design	Nr of pts	FU in months	Location (n)	Findings dental			screening %			Foci treatment						ORN n (%)
						Oral foci	Perio	Caries	Impac	P.a.	Other	Extr	Perio	Resto	Surg	Endo	Apex	
1976	Keys	R	246	-	Head and neck cancer	-	-	-	-	-	-	+	+	+	+	+	+	1 (0.4)
1976	Regezi	R	130	≥12	Nasopharynx (13) Oral cavity (101) Pharynx (3) Other (13)	-	25	-	-	-	-	+	-	+	-	-	-	22 (17)
1981	Horiot*	R	528	≥6	Nasopharynx (12) Oral cavity (155) Pharynx (167) Others (206)	-	-	-	-	-	-	+	-	+	-	-	-	4 (1)
1987	Epstein	R	146	60	Head and neck cancer (115) Others (31)	-	-	-	-	-	-	+	-	-	+	-	-	8 (5)
1989	Levendag	R	100	48	Oral cavity	20	-	-	-	-	-	+	-	-	+	-	-	2 (2)
1990	Brown*	R	92	-	Nasopharynx (7) Oral cavity (47) Pharynx (22) Others (22)	79	-	-	-	-	-	+	+	+	+	+	-	-
1992	Kumar	R	1140	48	Oral cavity	-	-	-	-	-	-	+	-	-	-	-	-	14 (1)
1994	Pochanugool	P	29 gel 22 rinse 22 both	44.1 30.9 43	Nasopharynx (50) Pharynx (4) Other (19)	-	-	-	-	-	-	+	-	+	-	-	-	-
1996	Niewald	R	52 HF 116 conv	34	Oral cavity (168)	-	-	-	-	-	-	+	-	+	+	-	-	23% HF 9% conv
1999	Epstein	R	57	-	Nasopharynx	-	-	-	-	-	-	+	-	-	-	-	-	1 (2)
2003	Sulaiman	R	187	22.1	Nasopharynx (29) Oral cavity (68) Pharynx (29) Other (61)	41	6	23	4	-	11	+	-	-	+	-	-	4 (2)
2004	Oh	R	55 extr 38 non-extr	33.5	Nasopharynx (17) Oral cavity (28) Pharynx (11) Other (37)	-	-	-	100	-	-	+	-	-	+	-	-	2 (4) 2 (5)
2006	Bonan*	P	40	28.7	Nasopharynx (2) Oral cavity (36) Pharynx (2)	-	65	30	-	-	-	+	+	+	+	-	-	5 (12.5)
2007	Ben-David	R	176	35	Oral cavity (152) Pharynx (20) Other (4)	-	-	-	-	-	-	+	-	-	-	-	-	0 (0)
2007	Chang	R	413	Median 45.6	Oral cavity Others	-	-	-	-	-	-	+	-	-	-	-	-	37 (9)
2008	Wang	R	181	-	Nasopharynx	-	-	-	-	-	-	+	-	+	+	+	-	0 (0)
2011	Schuurhuis	R	80	26	Oral cavity	75	54	10	16	19	4	+	+	-	+	-	+	9 (11)
2011	Studer	R	143 conv 161 RaDC	40 19	Oral cavity	73 53	-	-	-	-	-	+	+	+	-	+	-	3 (2) 2 (1)
2013	Bueno	P	9 healthy 19 perio	6	Oral cavity (18) Pharynx (4) Others (6)	-	0 100	-	-	-	-	+	+	-	-	-	-	-
2014	Duarte	R	158	-	Oral cavity (28) Pharynx (89) Nasopharynx (21)Others (20)	-	-	-	-	-	-	+	-	-	-	-	-	10 (6)

R= retrospective cohort study; P= prospective cohort study; Nr of pts= number of patients; FU in months= mean follow-up in months; ORN= osteoradionecrosis expressed as a percentage of the whole study group; Location= location of the tumor. Tumor location was grouped into 'oral cavity' (including oral cavity and oropharynx carcinoma), pharynx (including hypopharynx, pharynx, and larynx) and nasopharynx (nasopharynx and sinuses) as a separate group according to the radiation fields. All other tumor locations were grouped as 'others'. - = not described. += described. Percentages were rounded.
Horiot*: This study reported tumor location for 540 patients but the study group consisted of 528 patients. Numbers are presented here alike the article.
Brown*: This study reported tumor location for 98 patients, while a study group of 92 patients is described. Numbers are presented here alike the article.
Bonan*: This study included both dentulous and edentulous patients. Numbers presented in the table are a percentage of the total study group, including dentulous and edentulous patients.

Findings dental screening are presented as:
Oral foci= % of patients presenting with oral foci of infection
Impac= % of patients with impacted teeth or root tips
Perio= % of patients with periodontal disease
P.a.= % of patients with periapical problems
Caries= % of patients with carious lesions
Other= % of patients with other oral problems

Foci treatment is presented as:
Extr= tooth extraction
Surg= surgical removal of impacted teeth or root tips
Perio= periodontal treatment
Endo= endodontic treatment
Resto= restorative treatment
Apex= apexification

The incidence of dental fillings after treatment increased because of the oral sequelae resulting from radiation.

In another prospective study [24], 40 patients with squamous cell carcinoma in the head and neck region and with a low socioeconomic status received pre-radiation dental screening. Multiple teeth were extracted due to poor dental conditions and inadequate oral care. It could not be shown that extraction of poor teeth prevented ORN. ORN developed in the mandibles of 5 patients who were heavy users of tobacco and alcohol. These patients had received >63 Gy.

The prospective study by Bueno et al. [25] compared 2 groups of patients with malignant tumors of the upper aerodigestive tract subjected to radiotherapy. One group had periodontal disease (pockets 4-5 mm) and was treated accordingly. The controls were patients with a healthy periodontium and were not periodontally treated. Despite the radiation or chemoradiation, periodontal status improved in cancer patients subjected to pre-radiation periodontal treatment for up to 6 months after cancer treatment. Outcomes on ORN were not reported.

Retrospective studies
One retrospective study [26] compared head and neck cancer patients who had been subjected to a program of dental care with a historic control group treated with radiotherapy prior to the start of the dental care program. In the patients subjected to the dental care program, fewer extractions, fewer clinic visits, and less caries were reported. No data on ORN were provided.

Another study [29] assessed the relationship between ORN and tooth extractions by reviewing dental records of irradiated head and neck cancer patients. A greater risk of ORN was shown when teeth were extracted after radiotherapy. Of the patients who were subjected to post-radiotherapy extractions, 5% (3 out of 42) developed ORN as opposed to 7% (5 out of 92)(p=1.000) in patients who had extractions before radiotherapy. One retrospective study [32] reported on ORN incidence in a cohort of patients after dental screening and elimination of oral foci. ORN was observed in 14 out of 1140 patients (1%).

A third retrospective study [22] compared ORN frequency after hyperfractionated radiotherapy to conventionally fractionated radiotherapy (n=168 patients). Hyperfractionation led to an ORN frequency of 23%, compared to 9% in the conventionally treated group, whereupon hyperfractionation was discontinued.

A fourth retrospective study [35] compared two groups of head and neck cancer patients with impacted third molars: extraction (n=55 patients) and non-extraction (n=38 patients). Twelve patients were included in both groups as they had at least one, but not all, impacted molars removed before radiotherapy. The aim of this study was to determine how pre-irradiation extractions vs retention of impacted third molars affected the risk of ORN; 4 patients (2 in each group) developed ORN.

A fifth study [37] involved a cohort of head and neck cancer patients subjected to radiotherapy to determine whether pre-radiation elimination of oral foci could prevent ORN. Pre-radiation extractions were accompanied by a higher incidence of ORN compared to patients who did not have pre-radiation extractions (15% ORN vs 9%). The overall conclusion of that study was that pre-radiation extractions did not reduce the risk of ORN of the mandible following radiotherapy in dentate patients.

In three of the retrospective studies [2,36,39], patients were treated with intensity modulated radiation therapy (IMRT). In the other 17 studies, conventional radiotherapy was given. In the study by Ben-David et al. [2], strict prophylactic oral care in IMRT patients was evaluated. No ORN was found after a mean follow-up of 35 months. The IMRT-study by Studer et al. [36] evaluated minimally invasive oral care compared to conventional oral care in patients undergoing IMRT, using the ORN rate as outcome variable for efficacy of oral care. Based on their data, risk-adapted minimally invasive oral care was recommended before starting IMRT. ORN was seen in 2% of patients in the conventional oral care group after a mean follow-up of 40 months. In the minimally invasive group, 1% of patients developed ORN after a mean follow-up of 19 months.

The third IMRT study [39] compared dental health of head and neck cancer patients receiving IMRT compared to conventional radiotherapy. After dental screen-

ing, only patients without dental disease were included. Patients treated with IMRT exhibited significantly less ORN (0% vs 10%). The conclusion of this study was that the number of post-radiotherapy extractions has been reduced following the introduction of IMRT, even more so with a complete dental evaluation prior to radiotherapy.

Discussion

In our review, we found only low-level evidence to answer the questions of whether pre-radiation elimination of oral foci of infection in head and neck cancer patients is efficient and whether pre-radiation elimination of these oral foci should be mandatory. Most studies did not even use a univocal definition of an oral focus of infection, or it was unclear what was considered an oral focus.

Generally, an oral focus has been defined in the literature as 'a pathologic process in the oral cavity that does not cause major problems in healthy individuals, but may lead to severe (local or systemic) inflammation under certain circumstances' [3,4]. This definition does not indicate which pathology may lead to post-radiation oral problems such as ORN. One inclusion criterion for our review (Supplementary Table 2) was that a particular study should clearly define an oral focus of infection. Remarkably, in almost a quarter of the papers of which we read the full text, criteria for oral foci were not described. This resulted in the exclusion of those papers, even when the other inclusion criteria were met. Furthermore, when analyzing the included papers, we found no consensus about which foci of infection should be eliminated. This was due to the variety of definitions of an oral focus of infection (see Table 3). However, we did find agreement that "hopeless teeth" have to be extracted and "healthy teeth" have to be retained.

Another major issue that prevented us from drawing a more straightforward conclusion from the included papers was that the content of the dental screening performed was often not described clearly (Table 2). For example, most papers reported periodontal probing, but the periodontal examination was not clearly described. Moreover, in some papers periodontal probing was not described in the methods section, but probing, pocket depth and/or periodontitis results were described in the results, tables and figures. In these cases, we assumed that periodontal probing had actually been performed. This was also the case for furcation involvement, recession, plaque and mobility. Since radiotherapy may aggravate periodontal disease [40] or increase the risk of ORN [12], a full periodontal examination is advised as part of the dental screening, including probing depth, gingival recessions, mobility, furcation involvement, dental calculus, plaque and bleeding index.

Dental radiographs were often part of dental screening (Table 2). We advise to routinely make a panoramic radiograph, based on ALARA (as low as reasonably achievable) principles, to determine any impacted teeth, root tips, periapical problems, cysts and other radiological problems, as was done in 7 out of 19 studies. In addition, bitewings, periapical radiographs or both have to be made on indication.

Future studies in this field should therefore report in detail on how the dental screening was performed; otherwise the effects of dental screening on the post-radiation oral sequelae, such as ORN, cannot be assessed.

Although we gathered demographic data on age, tumor site, TNM-classification, histology, oncologic treatment and cumulative radiation dose during the assessment of the included studies (Supplementary Table 2), only tumor location is provided in Table 1 since the other data were reported in a great variety and could not be summarized in a compact table. In order to analyze the effects of pre-radiation elimination of oral foci of infection to prevent ORN, which etiology is multifactorial and not fully understood [41], there is a need for prospective studies with clearly described oncologic treatment modalities and well defined criteria for oral foci of infection. In addition, the studies should report which foci were eliminated and which oral sequelae occurred after radiotherapy. The follow-up period should at least be 2 years, since late side effects such as ORN take time to develop [3]. Moreover, the onset of ORN is influenced by many factors, including baseline dental hygiene, dental history, dental IQ, time between foci elimination and radiotherapy, post-radiation oral care, patient compliance to preventive post-radiotherapy regimens and genetics [41]. Unfortunately, these factors were not described in the majority of the included studies and could therefore not be analyzed.

In the majority of the included studies, patients were treated with conventional radiotherapy. However, in the last decade treatment modalities have changed substantially, for instance due to the introduction of IMRT around 2003 [42]. The exact effects of IMRT on the oral tissues and jaw bone in particular are not yet clear. It has been shown that IMRT results in less xerostomia due to sparing of the parotid and/or submandibular glands [43]. But at the same time, sparing of glands may result in higher doses to the other tissues in the radiation field, such as the jawbone [44]. These potentially higher doses to the jawbone increase the risk of developing ORN.

The reported outcomes in the included studies on occurrence of ORN after IMRT were limited due to a rather short follow-up [2,36]. Recently, a study was published with a longer follow-up (median of 37.4 months) [45] showing a low incidence of ORN (1%). However, 54% of the patients included in the latter study had a tumor located outside the oral cavity or oropharynx, resulting in a lower radiation dose to the jaws. This might be accompanied by a lower incidence of ORN. We therefore conclude that it is mandatory to assess the exact effects of IMRT on the oral tissues and jaw bone and the incidence of ORN.

Periodontal disease, either pre- or postradiotherapy [12,19,22], is possibly related to a higher risk of ORN. The effects of IMRT on periodontally diseased teeth should be further assessed, since many head and neck cancer patients with oral foci present with periodontal disease. Bueno et al. [25] evaluated the effects of pre-radiation periodontal treatment in patients with pockets of 4-5mm. Six

Table 2. Overview of the contents of the pre-radiation dental screening.

Author	Year of publication	X-ray		Periodontal probing	Furcation measurement	Gingival recession	Plaque	Mobility
		Performed	Type					
Keys	1976	+	-	+	+	-	-	+
Regezi	1976	+	-	+	-	-	-	-
Horiot	1981	+	Panoramic	+	-	-	-	-
Epstein	1987	-	-	+	-	-	-	-
Levendag	1989	+	Panoramic	+	-	-	-	-
Brown	1990	+	-	+	-	-	-	-
Kumar	1992	-	-	+	-	-	-	-
Pochanugool	1994	+	Full mouth	+	-	-	-	-
Niewald	1996	-	-	-	-	-	-	-
Epstein	1999	-	-	+	+	-	+	-
Sulaiman	2003	-	-	+	+	-	-	+
Oh	2004	+	Panoramic	+	+	-	-	-
Bonan	2006	+	Panoramic	+	-	-	-	-
Ben-David	2007	+	Panoramic	+	+	+	-	+
Chang	2007	+	Panoramic	+	-	-	-	-
Wang	2008	+	-	+	-	-	-	-
Schuurhuis	2011	+	Panoramic	+	-	-	-	-
Studer	2011	-	-	+	-	-	-	-
Bueno	2013	+	-	+	+	+*	+	+
Duarte	2014	+	Panoramic	+	+	+*	-	-

+ = described in study
- = not described in study
Panoramic= a panoramic x-ray was performed
Full mouth= a full mouth status of x-rays was made
* This study measured attachment level instead of gingival recession

months after radiotherapy, periodontal status had improved. However, the follow-up period of six months is too short to evaluate whether periodontal breakdown reoccurred and to evaluate whether periodontal treatment may increase the risk of ORN. All patients in this study received oral hygiene instructions, which would probably lead to improvement of the periodontal status. The study made no distinction between the effects of oral hygiene instructions and the effects of periodontal treatment. The results of initial periodontal treatment of teeth with pockets ≥6 mm in patients scheduled for radiotherapy are unclear and hardly any literature on this topic is available [40,46]. Thus, prognostic research designs might be useful to answer the question of whether or not teeth with pockets ≥6 mm should be removed or periodontally treated.

Another risk factor for ORN mentioned in various studies is alcohol/tobacco abuse [12,22,24,28,29,32,33]. Future studies might reveal that patients who use tobacco and/or alcohol abusively require extraction of their remaining teeth, due to the increased risk of developing ORN and the lack of compliance of many of these patients with oral hygiene instructions and caries prophylaxis.

The consensus in the dental field appears to be that a high level of oral hygiene is important during and after radiotherapy; oral hygiene instructions, removal of dental calculus and fluoride application were described in detail in the included studies. The study by Pochanugool [23] concluded that daily home fluoride application will prevent radiation caries. However, an increase of filling rate after radiation was reported, and extraction rate decreased. An increased number of fillings implies that more caries lesions occurred, although the authors concluded that fluoride application prevented radiation caries. Extraction rates will decrease if more teeth are preserved by filling. Consequently, it is difficult to interpret the results and conclusions.

Of the oral sequelae occurring after radiotherapy, ORN was most often reported (in 16 of 19 studies). Post-radiotherapy dental extractions (17 studies) were also described. Most studies (84%) did not report why post-radiotherapy extractions were needed. It would be valuable to know if all oral foci of infection were eliminated before the onset of radiotherapy, or if oral foci remained. The rationale for pre-radiation removal of oral foci can be justified only when such information is provided.

We included no randomized controlled trials in our systematic review. If only randomized controlled trials were accepted as appropriate evidence, then our research questions would have remained unanswered. By including prospective and retrospective cohort studies in this review, we aimed to answer the research questions, albeit with a lower level of evidence, to provide the field with up-to-date information on the assumed efficacy of pre-radiation elimination of oral foci of infection in head and neck cancer, and to point out the need for higher level of evidence from future well-designed and well-written studies.

Table 3. Definition of oral focus of infection.

Periodontitis	Advanced/severe periodontal disease [6,9,10,12-18,20,21,23-25]
	Furcation involvement [11,12,19,21,22]
	Mobility (with furcation involvement*) [11,12,20*,22,26]
	Periodontal disease pockets ≥6 mm [5,11,22,26]
	Active moderate periodontal disease [24]
	Advanced recession [22]
	Periodontal disease pockets ≥ 5mm [19]
Caries	(Deep*) caries (in which excavation may lead to pulpal exposure**) [5**,6,10*,12**, 13*-15,18,20**,21**,23*]
	Unrestorable carious teeth [9,16,17,19,20,22,25,26]
	Caries that extended to the gum line [22,26]
	Teeth with large, compromised restorations [22,26]
Pulpal pathology	Apical pathology [5,14,16-18,21,23,25]
	Nonvital teeth [6,17,23]
Radiographic findings	(Partially) Impacted teeth [5,12,16,17,20,21,25]
	Root tips (not fully covered by bone or showing radiolucency*) [5,6,12,20*,25]
	Incomplete eruption [6,20,21]
	Cysts [5]
	Radiographic abnormalities [5]

In summary, after systematically reviewing the literature, the efficacy of pre-radiation elimination of oral foci of infection on preventing oral sequelae remains unclear. We were also unable to find an unequivocal definition of an oral focus of infection and determine whether pre-radiation elimination of foci should be mandatory. This was due to a great heterogeneity in patient groups, dental screening techniques, definitions of oral foci of infection and techniques for eliminating these oral foci, and a lack of detail in the included studies on how screening on oral foci of infection was performed and what was considered as such an oral focus.

Notwithstanding the low level of evidence in the literature regarding the efficacy of screening and/or elimination of oral foci present, we hypothesize that the following should be considered as significant oral foci of infection and should be either effectively treated before onset of radiotherapy or be eliminated before onset of radiotherapy, when effective treatment of a particular focus of oral infection is not feasible:

- deep caries in which excavation may lead to pulpal exposure;
- active periodontal disease with pockets ≥ 6 mm, furcation ≥ grade 1, mobility > grade 1, gingival recession ≥ 6mm and especially a combination of these periodontal problems;
- non-restorable teeth with large restorations, especially those extending the gum line or with root caries, or those with severe erosion or abrasion;
- periapical granuloma and avital teeth;
- (partially) impacted or partially erupted teeth not fully covered by bone or showing radiolucency; cysts and other radiographic abnormalities.

To test this hypothesis, we recommend that future trials should include:

- a description in detail of what is considered to be an oral focus of infection;
- a description in detail of the treatment given to eliminate these oral foci of infection;
- a clear description of the content of the pre-radiation dental screening;
- a detailed description of patient and tumor characteristics, including age, tumor site, TNM-classification, histology, oncologic treatment, alcohol/tobacco use and cumulative radiation dose;
- a detailed description of the dental history and baseline dental status;
- an in detail description of the oral sequelae that occurred after head and neck radiotherapy
- the follow-up period should be >2 years to be able to detect late sequelae of radiotherapy.

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Chapter 3

Efficacy of routine pre-radiation dental screening and dental follow-up in head and neck oncology patients on intermediate and late radiation effects. A retrospective evaluation.

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Abstract

Background and purpose: Head-neck radiotherapy is accompanied by a life-long risk of developing severe oral problems. This study retrospectively assessed oral foci detected during pre-radiation dental screening and follow-up in order to assess risk factors for developing oral problems after radiotherapy.

Materials and Methods: Charts of 185 consecutive head-neck cancer patients, subjected to a pre-radiation dental screening in the University Medical Center Groningen, the Netherlands, between January 2004 and December 2008 were reviewed. Eighty (partially) dentulous patients scheduled for curative head-neck radiotherapy met the inclusion criteria.

Results: Oral foci were found in 75% of patients, predominantly periodontal disease. Osteoradionecrosis had developed in 9 out of 80 patients (11%). Overall, patients presenting with periodontal pockets ≥6mm at dental screening had an increased risk (19%) of developing osteoradionecrosis compared to the total group of patients. Patients in whom periodontal disease treatment was composed of initial periodontal instead of removal of the affected teeth, the risk of developing osteoradionecrosis was even higher, viz. 33%.

Conclusions: A worse periodontal condition at dental screening and initial periodontal therapy to safeguard these patients to develop severe oral sequelae after radiotherapy were shown to be major risk factors of developing osteoradionecrosis.

Introduction

Pre-radiation dental screening in head and neck cancer patients who will be subjected to radiotherapy to the head and neck region is aiming to locate oral foci in order to be able to eliminate these foci, thus preventing later irradiation-related oral complications, especially osteoradionecrosis (ORN) [1,2]. This approach is based on clinical experience and is hardly evidence-based [3,4]. Frequently, a short time period elapses between dental screening and the start of radiotherapy. This lack of treatment time available to eliminate foci of infection, can lead to radical decision-making in these patients. It is generally accepted that patients have to be free of dental foci 10-14 days before radiotherapy starts, in order to ensure initial healing of the oral tissues before radiotherapy. In 1992, Jansma et al [3] proposed a protocol for the prevention and treatment of oral sequelae resulting from head and neck radiotherapy, applicable in cancer centers operating with a dedicated dental team. The University Medical Center Groningen operates with a dental team consisting of an oral and maxillofacial surgeon (OMS), a hospital dentist and a dental hygienist. In our hospital, dental screening and dental treatment in head and neck cancer patients is performed according to this protocol [3].

Gortzak et al. [5] concluded that dental screening of patients is the current daily practice in Dutch hospitals, although there is little scientific evidence on its effectiveness. Moreover, wide variability between hospitals exists in the level of oral care that is provided to patients with head and neck cancer [5,6]. Recently, Rosales et al. [7] showed that dental examination before radiotherapy may prevent or minimize complications in the post-radiation period and may provide better post-radiotherapy oral health conditions in patients. Determining evidence based clinical guidelines for dental screening is considered mandatory in head and neck cancer patients. To assess whether such a screening is effective, a retrospective study was done in order to assess oral foci observed during pre-radiation dental screening and oral problems found during follow-up in head and neck cancer patients treated in our facility. In addition, we tried to identify risk factors, related to the oral problems as observed prior to radiotherapy for oral problems after radiotherapy.

Materials and Methods

A retrospective, descriptive study was conducted by reviewing the files of 185 consecutive adult head and neck cancer patients who had been subjected to pre-radiation dental screening for oral foci between January 2004 and December 2008 at the Department of Oral and Maxillofacial Surgery of the University Medical Center Groningen. Patients were included in this study, if they had undergone postoperative or primary curative radiotherapy or chemoradiation, as a part of primary cancer treatment for a carcinoma in the oral cavity or oropharynx. Patients

had to be (partially) dentulous at the time of the pre-radiation dental screening. A total dose of at least 40Gy had to be delivered to the mandible body by external beam radiotherapy. In general, the major salivary glands and a substantial part of the oral mucosa received a clinically relevant dose. Furthermore, a pre-radiation dental screening, including a panoramic radiograph and periodontal examination, should have been performed as well as a dental follow-up of at least 6 months after radiotherapy by the hospital's dental team. Patients were excluded if they had undergone previous radiotherapy to the head and neck region or if they were scheduled for brachytherapy.

Demographic data

General patient characteristics and potential confounding factors such as age, gender, tumor site, T- and N-stage, histology, oncologic treatment, alcohol consumption, tobacco smoking, and oral hygiene were collected from the patients' files.

Dental screening data

According to the standard procedures, every patient diagnosed with head and neck cancer was subjected to dental screening by a dental hygienist and a hospital dentist [3]. A panoramic radiograph and a periodontal status were routinely made in all patients. Oral hygiene instructions were given, adapted to the patient's needs. Dental foci were reported on and an individualized treatment plan was proposed by the dental team, including which foci had to be eliminated, depending on the estimated radiation dose. Eventually, the multidisciplinary team decided which foci had to be treated after discussion in a multidisciplinary team meeting consisting of an ablative surgeon, a radiation oncologist, a dentist and a dental hygienist.

Data on the oral foci found during dental screening were documented in the patient's file and collected for this study, as the following oral foci were taken into consideration: severe caries (defined as a carious lesion in which dentine excavation may lead to pulpal exposure, according to clinical and radiological judgment), periodontal disease (teeth with pockets ≥6mm), periapical dental pathology (periapical radiolucency on dental radiograph), (partially) impacted teeth, residual root tips, radiographic abnormalities (for example root resorption), and dental cysts [3].

The number of teeth present at dental screening was counted on the panoramic radiograph. The periodontal status was used to specify the number of deep (≥6mm) and shallow pockets (4-5mm). If the level of oral hygiene was documented, this was also used for analysis in this study. Oral hygiene level was based on subjective judgment of the oral hygienist, and scored as bad (plaque and bleeding index >60%), moderate (plaque and bleeding index 20-60%) or good (plaque and bleeding index <20%).

Treatment after dental screening before onset of radiotherapy

The pre-radiation dental treatment to eliminate oral foci was documented in the patients' files. The types of treatment were gathered for this study, being tooth extraction, periodontal treatment, apicoectomy, a combination of the previous treatments, or no treatment. The number of teeth extracted was determined using consecutive panoramic radiographs, if it was not clear from documentation only. Extracted teeth during ablative surgery, due to their proximity to the tumor, were also identified in this study.

From the patients' files, it was analyzed whether or not a patient was free of foci before radiotherapy. Due to lack of time, it was impossible to evaluate the outcome of initial periodontal treatment before the onset of radiotherapy, as usually established after 3 months in healthy patients. In this study, patients who had initial periodontal treatment for teeth with pockets ≥6mm, instead of tooth extraction, were not considered free of foci before radiotherapy started, since we did not know if these pockets did respond to periodontal treatment and if they were healed before radiotherapy started.

Furthermore, it was noted whether custom trays for the application of a fluoride gel had been made for the patients.

Radiotherapy

Until the end of 2007, the majority of patients were treated with 3D-CRT. Since 2008 patients were increasingly treated with IMRT. Radiotherapy was delivered using megavoltage equipment (6 MV linear accelerator). For all patients, a contrast-enhanced planning CT scan was made in supine treatment position.

Patients treated with concomitant chemoradiation therapy (CHRT) were irradiated with a conventional fractionation schedule (2Gy per fraction, five times per week up to 70Gy in 7 weeks). In case of primary radiotherapy of the more advanced tumors, which were considered ineligible for CHRT, an accelerated schedule with concomitant boost technique was used, either or not combined with cetuximab. These patients were treated with 6 fractions per week with a second fraction on Friday afternoon with a minimum interval of 6 h, up to a total dose of 70Gy in 6 weeks.

In patients treated with 3D-CRT, no attempts were made to spare the salivary glands. Most of these patients received bilateral elective irradiation of the neck nodes to a total dose of 46Gy and a boost on the primary tumor and pathological lymph nodes to a total dose of 70Gy.

IMRT treatments attempted to spare the parotid glands without compromising the dose to the target volumes. In general, 7-field equidistant, non-opposing beams were applied. All IMRT treatments applied a simultaneous integrated boost (SIB). Most patients received bilateral elective irradiation of the neck nodes to a total dose of 54.25Gy, in fractions of 1.55Gy. The primary tumor and pathological lymph nodes were treated to a total dose of 70Gy, in 2Gy fractions.

Chemotherapy was given concurrently with conventionally fractionated radiotherapy and consisted of carboplatin on day 1 (300-350 mg/m^2 in 30 min intravenously) and 5-fluorouracil (5-FU) from day 1 to 4 by continuous infusion (600 mg/m^2/24 h), consisting of 3 courses given with an interval of 3 weeks.

During radiotherapy

During radiotherapy patients were seen daily (Monday to Friday) by a dental hygienist. The patients' oral cavity was cleansed by spraying with saline according to protocol, and instructions were given to the patient to rinse their mouth with salt-baking soda solution at home [3]. If any oral problems occurred and/or treatment was needed during radiotherapy, these problems and its treatment were routinely documented in the patient's file. These data were used in this study. Furthermore, data on radiotherapy (start/end date, cumulative doses, type) were retrieved from the patients' files.

Follow-up

The follow-up period in this study, starting after the end of radiotherapy until the end of this study (December 2009), was at least 6 months. After radiotherapy, all patients visited members of the dental team (dental hygienist, dentist and/or OMS). The frequency of visits varied between patients, depending on the treatment need, patient compliance and oral hygiene level. Dental hygienist visits were focused on patients' oral hygiene and dental condition. Panoramic radiographs were made yearly in the study group according to protocol. If oral problems occurred, such as dental caries or periodontal breakdown, additional radiographs were made after discussion with the hospital's dentist or an oral and maxillofacial surgeon.

During the follow-up period, the following data were gathered from the files: number of new carious lesions (all new carious lesions reported, including initial lesions), progression of periodontal pocket depth (all cases where periodontal pocket depth, measured with a periodontal probe, increased when pathological pockets were present (>3mm)), periapical problems discovered on radiographs, number of tooth extractions, incidence of oral candidiasis, incidence of ORN (exposed bone trough an opening in the overlying mucosa, persisting as a non-healing wound for three months or more [8], level of oral hygiene (bad, moderate, good), frequency of fluoride application, patients' complaints about a dry mouth (xerostomia) and clinical signs of a dry mouth.

Statistical analysis

Data were explored, using descriptive statistics and graphs, in SPSS 16.0. Normality was tested using Q-Q plots. Risk analysis was done using Chi square test and Fisher's exact test. Values of $p < 0.05$ were considered significant.

Table 1. Demographic and clinical characteristics of the study group (n=80).

Variable	Category	Number of patients	%
Age, years	Mean	58	
	Range	20-89	
Gender	Male	43	54
	Female	37	46
Tumor site	Oral cavity	70	88
	Oropharynx	10	12
T- classification	T1	18	23
	T2	19	23
	T3	9	11
	T4	17	21
	Tx	17	22
N-classification	N0	29	36
	N1	14	18
	N2	21	26
	Nx	16	20
Histology	Squamous cell carcinoma	54	68
	Other	26	32
Treatment plan	Radiotherapy	13	16
	Radiotherapy + Surgery	58	73
	Radiotherapy + Chemotherapy	9	11
Chemotherapy type	Carboplatin/5-FU	7	9
	Cetuximab	2	2
	No chemotherapy	71	89
Functionally inoperable	Yes	8	10
	No	72	90
Alcohol consumption	Patient drank alcohol in the past, amount unknown	4	5
	Patient never drank alcohol	10	13
	Patient drinks ≤ 2 drinks p.d	27	34
	Patient drinks > 2 drinks p.d	19	23
	Not reported*	20	25
Smoking	Patient smoked in the past, amount unknown	22	28
	Patient has never smoked	15	19
	Patient smokes ≤ 1 pack of cigarettes p.d.	8	10
	Patient smokes > 1 pack of cigarettes p.d.	19	23
	Not reported	16	20
Oral hygiene level	Bad	19	24
	Moderate	21	26
	Good	18	22
	Not reported	22	28

p.d.= per day

*Not reported= data were not reported

Results

Eighty patients met the inclusion criteria (figure 1). Mean follow-up time was 26 months (range 6-69 months). Patients received a mean radiation dose of 64Gy to the primary tumor site (range 50-70 Gy). Twenty-seven patients died during follow-up due to tumor-related causes. Demographic and clinical characteristics of the patients are summarized in table 1.

Pre-radiation: dental screening and treatment of oral foci

Oral foci were diagnosed in 60 out of 80 patients (75%). The types of oral foci at dental screening were periodontal pockets ≥6mm (43 patients), periapical dental pathology (15 patients), severe caries (8 patients), impacted teeth (7 patients), residual root tips (6 patients) and radiographic abnormalities (3 patients). Since one patient can be diagnosed with more than one oral focus, the sum of the numbers is higher than 60.

Tooth extraction

Extraction of teeth to eliminate oral foci was performed in 56 patients. An average of 7.7 teeth was extracted per patient. In 13 patients extractions were combined with periodontal treatment to other teeth. In the remaining 43 patients teeth were extracted because of periodontal pockets ≥6mm (25 patients), severe caries (8 patients), a combination of severe caries and periodontitis (3 patients) or for other reasons (7 patients) (figure 2). In addition, in 11 patients teeth were removed because of a close proximity to the tumor during ablative surgery.

Periodontal treatment

Forty-three (75%) out of the 60 patients had periodontal pockets ≥6mm. Periodontal treatment was performed in 15 out of these 43 patients, often combined with tooth extractions (13 patients) in order to eliminate the oral foci (figure 2). Periodontal treatment was performed before radiotherapy, but the effects of periodontal treatment could not be effectively evaluated due to lack of time before radiotherapy. Therefore, these 15 patients were not considered to be free of foci before radiotherapy started.

Smoking and alcohol consumption

Data on smoking habits and alcohol consumption are summarized in table 1.

Fluoride trays

Fluoride trays were made before radiotherapy in 64 out of 80 patients. The other 16 patients received full mouth extractions before radiotherapy. Patients who received fluoride trays were informed on their use by a dental hygienist. A 1% neutral sodium fluoride gel was prescribed to be used every second day; this regimen was based on the studies by Jansma et al [6,9].

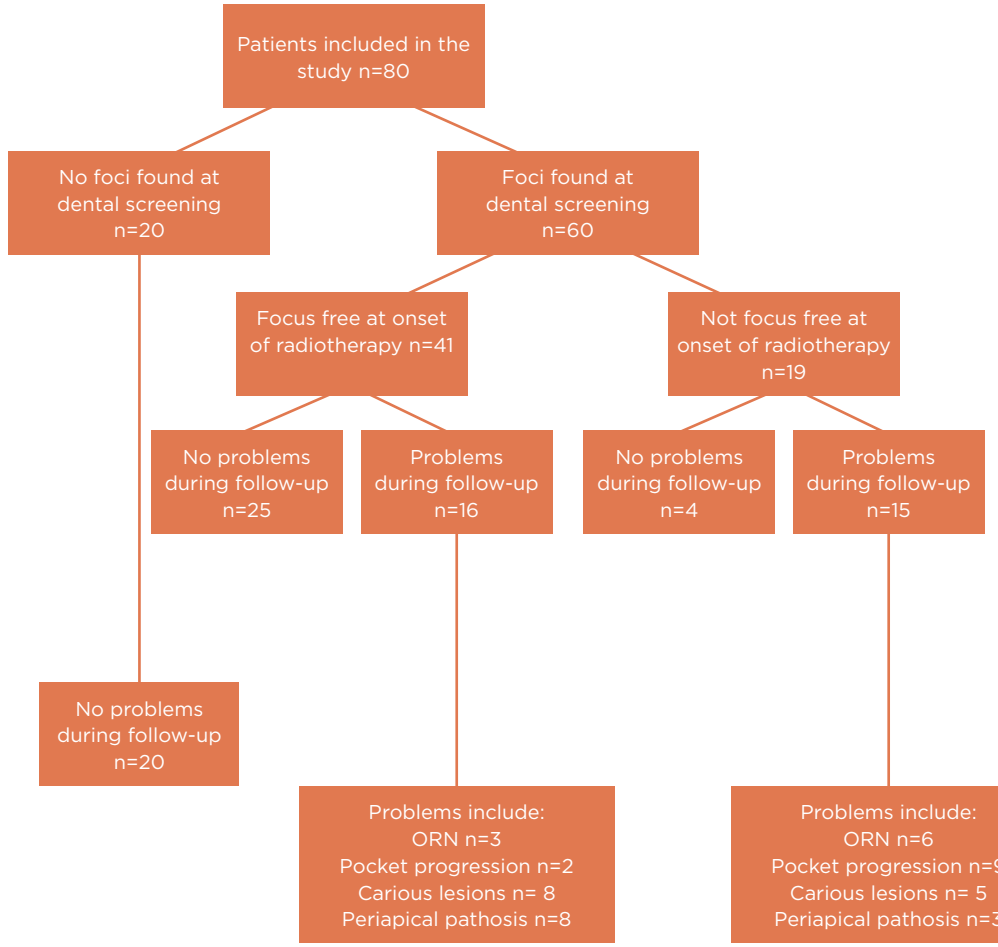

Figure 1. Flow chart showing the results of dental screening and the results of follow-up.
Since one patient could be diagnosed with more than one oral problem, the sum of the number of problems is higher than the number of patients.

Oral problems observed during radiotherapy

During radiotherapy, oral Candidiasis was reported in 14 patients. Treatment consisted of antifungal lozenges (amfotericine B 10mg, q.d.).

Post-radiation: problems during follow-up

During follow-up, 31 out of 80 patients (39%) developed oral problems (figure 1). The oral problems comprised of osteoradionecrosis (ORN), progression of periodontal pockets, development of one or more carious lesions, and periapical pathosis (figure 1).

Osteoradionecrosis

Osteoradionecrosis (ORN) developed in nine patients (11%) (table 2). All regions in which ORN developed had received a cumulative radiation dose >40Gy. More smokers were seen among patients who developed ORN (78%) than among non-ORN patients (36%; p = 0.029) resulting in an OR of 6.1 [CI 1.2-32.4] for a higher risk of developing ORN in smokers.

Patients who presented with periodontal disease (pockets ≥6mm) at dental screening had a significantly higher risk of developing ORN during follow-up than patients without periodontal disease (p = 0.033). It has to be noted, however, that in 7 out of 9 patients ORN developed in an area in which teeth had been removed because of severe periodontal disease. Severe caries, periapical problems, residual root tips, impacted teeth, and radiographic abnormalities at the time of dental screening were not found to be a risk factor for developing ORN in our study.

Of the 43 patients presenting with periodontal disease (pockets ≥6mm) at dental screening, 15 patients were considered not free of oral foci as treatment (partly) consisted of initial periodontal therapy and not the removal of these teeth. Among these 15 patients, 5 developed ORN, suggesting that the chance of developing ORN, when periodontal pockets ≥6mm are not aggressively treated, is highly increased, viz. 33% in this study.

In 3 out of 9 patients, post-radiotherapy extractions were done in the region where ORN developed because of pain with endodontic origin in 2 patients, and pain from a root tip in 1 patient.

What is remarkable is that none of the patients who were judged to be free of oral foci at the dental screening developed ORN (figure 1).

Post radiotherapy pocket progression

In 14 patients (18%), progression of periodontal pocket depth was observed during follow-up. In 3 of these 14 patients periodontal pockets 4-5 mm were present at dental screening and progressed during follow-up. In 11 of these 14 patients periodontal pockets ≥6mm were already present at dental screening. In 6 out of 11 patients initial periodontal therapy was combined with tooth extractions. In 4 out of 11 patients teeth were extracted without initial therapy (in 2 of these 4 patients some teeth with pockets ≥6mm were left, in the other 2 patients all teeth with pockets ≥6mm had been extracted). In 1 out of these 11 patients initial periodontal therapy was performed without extractions.

After pocket progression was observed, treatment consisted of further initial therapy, tooth extraction or individualized oral hygiene instructions.

Caries

Thirteen patients (16%) developed one or more carious lesions. All these carious lesions developed within 2 years after radiotherapy.

Table 2. Characteristics of patients with osteoradionecrosis (n=9).

Variable	Category	Number of patients	%
Age, years	Mean	58	
	Range	49-74	
Gender	Male	6	67
	Female	3	33
Tumor site	Oral cavity	6	67
	Oropharynx	3	33
Treatment plan	Radiotherapy	1	11
	Radiotherapy + Surgery	5	56
	Radiotherapy + Chemotherapy	3	33
Cumulative dose on the mandible	Mean	66 Gy	
	Range	60-70	
Cumulative dose ORN region	Mean	61 Gy	
	Range	40-69	
T- classification	T1	3	33
	T3	2	23
	T4	3	33
	Tx	1	11
Alcohol consumption	Yes	7	78
	No	2	22
Smoking	Yes	6	67
	No	3	33
Type of foci	Pockets ≥6 mm	8	89
	Severe caries and residual root tips	1	11
Treatment of foci	Tooth extraction	4	44
	Periodontal treatment and tooth extraction	5	56
Free of foci before start RT	Yes	3	33
	No	6	67
ORN region	Mandible	8	89
	Maxilla	1	11
ORN onset in months after RT	Mean	13.5	
	Range	3-31	
Extraction in ORN region	Pre- RT	8	
	Post RT*	3	

ORN = osteoradionecrosis
RT = radiotherapy
* Reasons for post-radiotherapy extractions were an untreated oral focus, which was a periodontally affected molar (pockets 7 mm), pocket progression in a patient who had pockets ≥6mm at dental screening and was periodontally treated combined with tooth extractions, and a residual root tip, remaining after pre- radiotherapy tooth extraction in a patient who had pockets ≥6mm at dental screening and was periodontally treated combined with tooth extractions. In all 3 patients, ORN developed in the area where extractions had been performed post-radiotherapy.

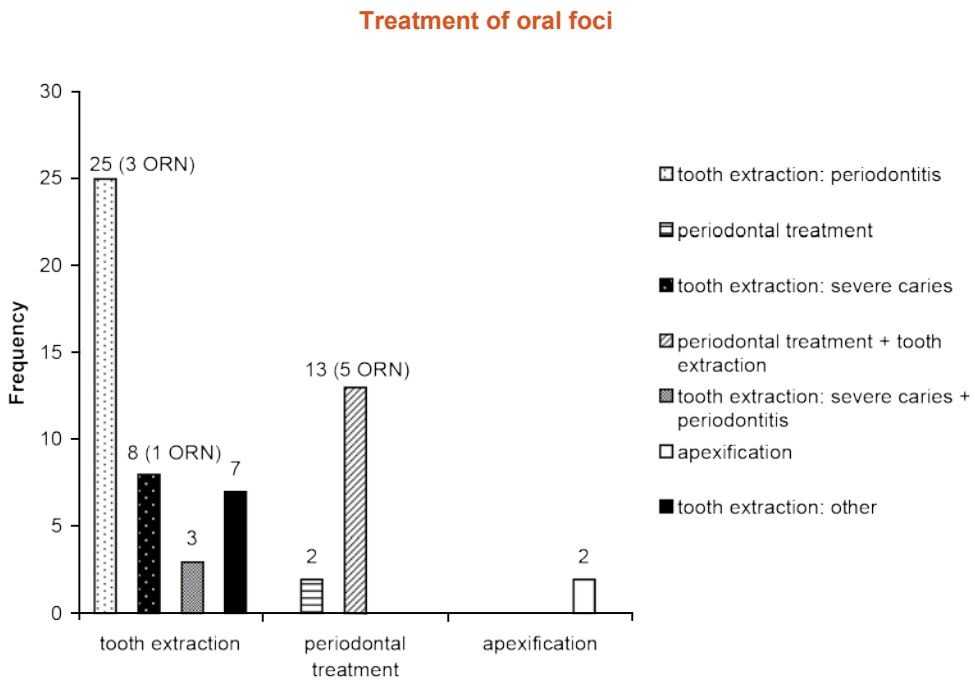

Figure 2. Treatment of the oral foci after dental screening.
Tooth extractions were needed in 43 patients because of severe periodontitis (pockets ≥6mm), severe caries, a combination of severe caries and periodontitis and for other reasons in 7 patients. Sixteen patients had a full mouth clearance after dental screening, including the 3 patients who had tooth extractions because of a combination of severe caries and periodontitis, 9 patients with severe periodontal breakdown, and 4 patients in the group 'other'. The association between type of treatment and number of patients within that group that developed ORN is indicated between brackets.

Post radiotherapy periapical pathosis

Eleven patients (14%) developed periapical pathosis during follow-up, discovered on radiographs. In 8 out of these 11 patients periapical problems were not found at the time of dental screening, but developed during follow-up. In the other 3 patients, periapical lesions had been left untreated after dental screening. Further treatment consisted of endodontic treatment in 4 patients, tooth extraction in 2 patients and in 5 patients, who had no complaints, an expectative policy was followed.

Level of oral hygiene, fluoride prophylaxis and xerostomia

Shortly after radiotherapy, 16 patients (25%) reported discontinuation of their use of fluoride trays. Reasons for not using the trays mentioned in the patients' files were: it was too painful to use the trays or the fluoride gel was irritating the oral mucosa (10 patients). Six patients stated having not understood that they had to continue to use the trays after radiotherapy had ended. In these 16 patients, the oral hygiene level was good in 4 patients, moderate in 6 patients, bad in 5 patients, and was not reported in 1 patient.

Fifty-five patients (69%) out of the 64 patients of whom data of a dry mouth and clinical signs of a dry mouth were available, did complain of a dry mouth. In all these patients, clinical signs of a dry mouth were observed and reported by the clinician in their files shortly after radiotherapy. One year after radiotherapy, similar findings were observed in 38 patients (88%) out of the 43 patients of whom data were available on complaints of a dry mouth and clinical signs of a dry mouth.

Discussion

About 75% of the head and neck cancer patients subjected to a pre-radiation dental screening have oral foci that need treatment when head and neck radiotherapy is scheduled. The majority of these foci encompassed periodontal decay, as periodontal pockets ≥6mm were observed in most of the patients. This is a rather significant observation as our analysis revealed that particularly these patients were prone to developing ORN.

ORN is a late side effect of radiotherapy which is hard to treat [2]. Prevalence of ORN in patients treated with conventional radiotherapy is 7.4% [CI 4.8-10] [10]. In this study we diagnosed ORN in 9 out of 80 patients (11%) occurring on an average of 13.5 months after radiotherapy (range 3-31 months). The patient who developed ORN after 3 months, which is considered very early, developed ORN in a mandibular area reconstructed with an iliac crest bone graft, not related to dental pathology. Eight out of nine ORN patients were diagnosed with severe periodontal disease at dental screening. Periodontal disease and an increased risk of developing ORN seemed to be associated. In fact, if existing periodontitis was not aggressively treated before radiotherapy ORN developed in 33% of these patients. The association between periodontitis and the development of ORN has to be assessed in future studies, as the acidic oral environment after radiotherapy is in general especially thought to be prone to development of dental caries and oral infections [11-14]. Such an acidic oral environment is not an environment in which periodontal pathogens are likely to survive. However, in periodontal pockets the pH might be dissimilar from the pH in the oral cavity and thus be more favorable for periodontal pathogens.

The majority of patients with oral foci in our study had periodontal disease (75%). This was also reported in other recent articles [15,16]. Unfortunately, a number of oral foci marked by our dental team appeared not to be eliminated before radiotherapy. In the far minority of the cases this was due to an oral focus that was missed before the onset of radiotherapy, but in the far majority this violation of the protocol was related to a too short period between diagnosis of periodontal disease and start of radiotherapy to allow for a proper evaluation of the effect of initial periodontal therapy. Also prosthodontic considerations were noted, that led

to the preservation of periodontally compromised teeth to enhance retention of prosthetic devices thought essential for oral functioning.

The results of initial periodontal treatment in patients scheduled for radiotherapy of teeth with pockets ≥6mm are unclear and hardly any literature on this subject is available [17,18]. As particularly in this group of patients a rather high number of ORN cases developed, it has to be assessed in future studies whether all severely periodontal diseased teeth do have to be removed before radiotherapy and if initial periodontal therapy is not a proper alternative treatment modality to eliminate periodontal disease in this type of patients. The latter might be due to the nature of the oral flora present in the pockets with bone destructive properties, as well as that maintaining teeth with periodontal pockets ≥6mm after radiotherapy may put the patient at risk for post-radiotherapy extractions. With regard to this assumption one has to bear in mind that periodontal disease progressed in the majority of the patients after radiotherapy.

Decisions to remove teeth that are considered a focus can be complex, especially because dental awareness is increasing and patients sometimes refuse tooth extractions. In addition, a larger part of the population is dentulous nowadays, and therefore, more head and neck cancer patients are dentulous. Where doubtful teeth used to be extracted in patients subjected to radiotherapy to the head and neck region, it is often decided nowadays to save (some of these) teeth for prosthetic use. The results of our study suggest that remaining doubtful teeth for prosthetic use might put patients at an increased risk of developing ORN.

Smoking and alcohol abuse are well known risk factors for developing oral cancer [19,20]. In the literature, it has been suggested that vasoconstriction caused by smoking enhances the risk of developing ORN [19]. In accordance with these findings, in this study the highest risk on developing ORN was observed in smoking patients. However, it has to be noted that data on smoking habits could not be retrieved from all the files.

Because of the usually irreversible irradiation-induced reduction of salivary flow [11,12,21-23], head and neck radiotherapy patients possess a life-long risk of developing so-called radiation caries [24]. Nevertheless, it was documented in the patients' files that some patients stopped using fluoride trays because the fluoride gel was reported to be irritating the oral mucosa, or because it was not clear to them that the use of fluoride trays had to be continued after radiotherapy ended. Neutral fluoride gels were prescribed which have to be made by the pharmacist, but it seems that some pharmacists provided the patient with an over the counter acidified gel. Not only can this acidic gel be very irritating on the oral mucosa during radiotherapy, because the integrity of the oral mucosa is damaged by radiotherapy (mucositis), it also can cause dental erosion since irradiated patients often have a reduced salivary flow and therefore less buffer capacity. The clinician can learn from these findings that oral hygiene instructions should be repeated frequently, since patients tend to forget the information that had been given, and the patient should be motivated repeatedly.

Currently, head and neck cancer patients are treated according to a protocol, but no standardized protocol is used for documentation of data. Therefore, a number of data were missing that limited the interpretation of the results of our retrospective study. Another limitation of this study was that over 25% of the patients died after a relatively short follow-up period. In these patients, only early side effects of radiotherapy could be evaluated.

In this study oral foci were common in head and neck cancer patients seen for a dental screening. Oral foci that were left untreated or that were not proven adequately resolved before start of radiotherapy increased the risk on post radiotherapy tooth extraction and thus the risk of developing ORN. The results of our retrospective analysis suggest that particularly patients with severe periodontal disease were prone to develop ORN, particularly when the periodontally affected teeth in these patients were not (aggressively) treated. Therefore, a prospective study is needed to assess the relation between periodontal disease and the risk of development of ORN. Besides the risk of ORN due to leaving strategic teeth with periodontitis, risk of ORN by removing these teeth and the functional gain must be taken into account. In addition, the efficacy of the treatment modalities used for eliminating oral foci pre-radiotherapy, especially in patients with periodontitis, has to be further assessed.

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Chapter 4

Head and neck intensity modulated radiation therapy leads to an increase of opportunistic oral pathogens

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Abstract

Objectives: The recent introduction of intensity modulated radiation therapy (IMRT) has led to new possibilities in the treatment of head and neck cancer (HNC). Limited information is available on how this more advanced radiation technique affects the oral microflora. In a prospective study we assessed the effects of various advanced treatments for HNC on the oral microflora, as well as the effects of elimination of oral foci of infection.

Materials and Methods: All consecutive dentate patients >18 years, diagnosed with a primary oral or oropharynx carcinoma and seen for a pre-treatment dental screening between May 2011 and May 2013, were included. Patients were grouped by oncologic treatment: surgery (SURG), IMRT (IMRT) or IMRT+chemotherapy (CHIMRT). Dental screening data, demographic data, subgingival biofilm samples, oral lavages and whole saliva samples were obtained to microbiologically analyze the effects of cancer treatments (1 year follow-up).

Results: This study included 82 patients (29 SURG, 26 IMRT and 27 CHIMRT). The trends in changes in prevalence and proportions of microorganisms were comparable in the IMRT and CHIMRT group. However, relative to the SURG group, increased prevalence of enteric rods, staphylococci and *Candida* species was observed in the IMRT and CHIMRT groups. In these groups, elimination of oral foci decreased the frequency of detection of pathogens such as *P. gingivalis, T. forsythia* and *S. mutans*.

Conclusion: Different treatments in HNC patients result in different changes in the oral microflora. Opportunistic pathogens such as staphylococci, enteric rods and *Candida* species tend to increase in prevalence after IMRT with or without chemotherapy, but not after surgical intervention.

Introduction

Head and neck cancer (HNC) patients treated with radiotherapy (RT) have a lifelong risk of developing severe oral problems. These patients may suffer from loss of salivary gland function, which predisposes them to secondary problems such as rapidly progressing dental caries and fungal and bacterial infections [1-3]. Radiation-induced hyposalivation and subsequent dental caries are associated with an increased risk for dental extractions and development of osteoradionecrosis (ORN) [4]. To prevent ORN and other oral sequelae after radiotherapy, pre-radiation dental screening is commonly performed to locate and eliminate oral foci of infection, although the efficacy of these interventions is unclear [5].

During the last decade, treatment techniques in HNC have changed substantially, due to the introduction of intensity modulated radiation therapy (IMRT) and concomitant chemoradiation [6]. The differences between 3D conformal radiotherapy (3D-CRT) and IMRT, with or without chemotherapy, have not been studied regarding their effects on oral microflora. For example, the reduced salivary secretion observed after IMRT relative to 3D-CRT may result in a less acidic oral environment and a lower incidence of hyposalivation-induced dental caries [7]. Teeth might be preserved longer after IMRT, since a less acidic environment may be less prone to induce and promote dental caries. As a consequence, longer survival of teeth provides more time for periodontal pathogens to cause periodontal problems. This might explain why recently periodontal pocket progression in irradiated patients was seen [8].

Although IMRT reduces the risk of xerostomia, it is not known whether the effects on the oral microflora are similar or different compared to changes induced by 3D-CRT. Changes related to 3D-CRT have been described for both the short term (<1 year) [9-12] and long term (≥1 year) [13-15]. In general, microorganisms associated with oral disease increased in time after RT. This was related to salivary secretion rate and buffering capacity [14]. Only short-term effects (during 6 weeks of RT) of IMRT have been reported for a small sample of patients [16]. The latter study showed that IMRT is more conducive to maintaining the relative stability of the oral ecosystem than 3D-CRT. To the best of our knowledge long term (>1 year) effects of IMRT on oral microflora have not been described so far. Since loss of salivary secretion is less after IMRT than after 3D-CRT, it is worth studying whether this results in less pronounced alterations to the oral flora. Due to ethical considerations, it is not possible to compare 3D-CRT with IMRT prospectively. Therefore, we conducted a prospective study to assess the effects of three advanced HNC treatments—surgery, IMRT and IMRT with chemoradiation—on the oral microbial composition with a follow-up of 1 year. Also, the effects of elimination of oral foci of infection on the oral microbial composition in patients subjected to IMRT or IMRT and chemoradiation were assessed.

Materials and Methods

Patients

All consecutive dentate or partially dentate patients >18 years, diagnosed with a primary oral cavity or oropharynx carcinoma, who were referred to the Department of Oral & Maxillofacial Surgery of the University Medical Center Groningen (UMCG) in the Netherlands for a pre-treatment dental screening between May 2011 and May 2013, were included in this study. To be eligible for this study, post-oncologic treatment microbial follow-up had to be available for at least 6 months. Treatment plans of all patients were discussed in the multidisciplinary tumor board of the UMCG. Patients were placed into one of three groups according to their oncologic treatment: 1) intensity modulated radiation therapy (IMRT), 2) IMRT concurrent with chemotherapy (CHIMRT) or 3) surgery (SURG). Patients who had undergone previous surgical removal of a tumor and/or RT and/or chemoradiation to the head and neck region were excluded, as were patients with an unknown primary or parotid gland tumor. The medical ethical committee of the University Medical Center of Groningen approved the study protocol (METC 2012/091).

Surgery group

The surgery group consisted of patients who received oral oncologic surgery (SURG), not followed by IMRT or CHIMRT. Patients eligible for oncologic surgery were operated according to the guidelines of the Dutch Head & Neck Society (NWHTT) [17].

Radiotherapy and chemoradiation groups

The radiotherapy group (IMRT) consisted of patients who were subjected to definitive primary or post-operative IMRT. The chemoradiation group (CHIMRT) consisted of patients who were subjected to definitive primary or post-operative CHIMRT.

IMRT was delivered using megavoltage equipment (6 MV linear accelerator). For all patients, a contrast-enhanced planning CT scan was made in supine treatment position. Patients received a conventional fractionation schedule of 2 Gy daily, five times per week up to 70 Gy on the primary tumor and pathological lymph nodes in 7 weeks or an accelerated schedule with 6 fractions per week. Elective lymph node areas in the neck (both sites) were irradiated with a dose of 54.25 Gy, in fractions of 1.55 Gy. IMRT treatments attempted to spare the parotid glands without compromising the dose to the target volumes. In general, 7-field equidistant, non-opposing beams were applied. The radiation dose was delivered using a simultaneously integrated boost IMRT technique.

Chemotherapy was given concurrently with fractionated IMRT and consisted of Carboplatin on day 1 (300–350 mg/m^2 in 30 min intravenously) and 5-fluorouracil (5-FU) from day 1 to 4 by continuous infusion (600 mg/m^2/24 h), consisting of 3 courses given with an interval of 3 weeks. Postoperative chemotherapy consisted of 6x50 mg Cisplatin weekly. When chemotherapy was considered to be infeasible, patients were treated with cetuximab using a loading dose of 400 mg/m^2 one week prior to radiotherapy and a weekly dose of 250 mg/m^2 during radiotherapy.

Dental screening

All patients were evaluated before their oncologic treatment as part of routine clinical practice by means of an oral and dental screening, including radiographic examination. This screening is based on the protocol published by Jansma *et al.* [18]. Oral foci of infection were defined as follows [5]:

- deep caries in which excavation may lead to pulpal exposure;
- active periodontal disease with pockets ≥6mm, furcation ≥grade 1, mobility >grade 1, gingival recession ≥ 6mm and especially a combination of these periodontal problems;
- non-restorable teeth with large restorations, especially those extending beyond the gum line or with root caries, or those with severe erosion or abrasion;
- periapical granuloma and avital teeth;
- impacted, partially impacted or partially erupted teeth not fully covered by bone or showing radiolucency;
- cysts and other radiographic abnormalities.

To quantify periodontal disease, the periodontal inflamed surface area (PISA) was used [19]. Patients were asked about their smoking and drinking habits. Self-reported smoking options were ‘current smoker’, ‘past smoker’, or ‘never smoked’ and self-reported alcohol consumption options were ‘never drink alcohol’ or ‘drink alcohol’.

Additionally, baseline oral lavage, subgingival biofilm samples and unstimulated and stimulated whole saliva samples were taken at the dental screening. All data obtained at baseline and follow-up visits were collected in a predetermined order and recorded using a standardized study form designed for this study.

Sampling methods

At various time points, an oral lavage [20] and subgingival biofilm samples [21] were obtained for microbiological evaluation. The total anaerobic bacterial count as well as detection frequencies and bacterial load of the periodontal pathogens *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia, Parvimonas micra, Fusobacterium nucleatum,* and *Campylobacter rectus* were determined in subgingival biofilm samples. Total aerobic bacterial count and detection frequencies and bacterial load of *Streptococcus mutans,* lactobacilli*, Actinomyces* species, Gram negative enteric rods and *Candida albicans* were determined in the oral lavage samples. Microbiological analysis of the samples was performed by the Oral Microbiology Laboratory of the UMCG, according to standard laboratory procedures [20-22]. Unstimulated and stimulated whole saliva samples were taken at the same time points.

Whole saliva samples
Unstimulated whole saliva samples were collected over a period of 5 minutes in a sterile vial. Before the start of sampling, the empty vial was weighted on a pocket size scale in grams with 2 decimals to 0.01 gram. Patients were seated in a quiet room and asked to bend their head forward slightly. A timer was set for 5 minutes. They were allowed to spit the saliva that had collected on the floor of the mouth into the vial whenever they needed to spit. After 5 minutes, they were asked to empty their mouth by spitting into the vial once more. The vial was then weighted again. The salivary flow rate in ml/min was calculated by subtracting the weight of the empty vial from the weight of the vial after the collection period and dividing it by 5. The same procedure was followed to obtain stimulated whole saliva samples, but now the patients were asked to chew on a piece of parafilm (5x5 cm) for 5 minutes. Once again, they spit the saliva that had collected in the mouth into a sterile vial.

Hyposalivation was defined as a resting whole saliva flow rate ≤0.1 ml/min and/or a stimulated whole saliva flow rate of ≤0.5 ml/min [23].

Treatment of oral foci of infection
Treatment of oral foci of infection was performed for patients expected to undergo IMRT or CHIMRT as part of oncologic treatment [5]. In surgically treated patients, teeth with a very bad prognosis were extracted before or during oncologic surgery. Before the onset of IMRT or CHIMRT, patients were seen by a dental hygienist for dental prophylaxis and oral hygiene instructions. Elimination of oral foci was done at least 10 days before the onset of radiotherapy to allow possible tooth extraction wounds to heal [18,24].

Oral care during IMRT
During hospital admission after oncologic surgery, patients were seen daily by a dental hygienist for spraying of the oral cavity according to standard protocol [25]. During IMRT and CHIMRT, the spraying was combined with instructions to rinse the mouth with a salt-baking soda solution at home, 8-10 times per day [18]. Dentate IMRT and CHIMRT patients received custom-made fluoride trays and were prescribed a neutral fluoride gel to be used every second day [26,27].

Follow-up
Regular follow-up visits to the oncology surgeon, dental hygienist and/or hospital dentist were combined with visits to the researcher (JMS) to collect study data.

SURG patients were seen at dental screening and at 6 months and 1 year after surgery. IMRT and CHIMRT patients were seen at five time points: at dental screening, before onset of IMRT/CHIMRT (usually on the 1st day of IMRT), and 6 weeks, 6 months and 1 year after IMRT/CHIMRT.

Statistical analysis
All data (dental screening and follow-up visits) were recorded using a study form designed for this study. Dental hygienists were instructed by the researcher on how to use the study form. Demographic data were retrieved from the patient files. Data were analyzed using SPSS Statistics 22. Values of $p<0.05$ were considered significant.

Comparison between the 3 treatment groups at baseline, 6 months and 1 year of follow-up was done using Kruskal-Wallis tests for quantitative data (age, proportions of microorganisms, salivary flow rate) and Chi-square tests for binary data (gender, prevalence of microorganisms). The percentage of each specific microorganism was given as a proportion of the total anaerobic count. For calculation of the means, we used culture positive patients only. Comparing baseline and 1 year data within a group was done using Wilcoxon signed rank test.

Testing for significant differences in prevalence and proportions of microorganisms within and between the treatment groups was done for all cultured microorganisms. Only the statistically significant different values were reported in the results section. Regarding the other factors of influence on oral microflora composition, again only the statistically significant different values were reported in the results section.

Results

Demographics
Eighty-nine patients met the inclusion criteria. Patients who had full mouth dental extractions to eliminate oral foci of infection (n=7) were excluded from analysis. The final study population therefore consisted of 82 patients who were grouped by oncologic treatment modality (Table 1). Follow-up was 1 year for all patients, except for 2 IMRT-patients who were lost to follow up after 6 months due to metastatic disease. No statistically significant differences between the groups were present at baseline.

Subgingival total bacterial counts
The subgingival total bacterial count decreased from $1.9x10^8$ cfu/ml at baseline to $0.53x10^8$ cfu/ml after 6 months ($p<0.001$) in the IMRT group, and from $1.9x10^8$ cfu/ml at baseline to $1.6x10^8$ cfu/ml after 6 months ($p=0.014$) in the CHIMRT group.

The subgingival total bacterial counts decreased from $1.5x10^8$ cfu/ml at baseline to $0.46x10^8$ cfu/ml after 1 year ($p=0.032$) in the SURG group, from $1.9x10^8$ cfu/ml at baseline to $0.19x10^8$ cfu/ml after 1 year ($p=0.001$) in the IMRT group, and from $1.9x10^8$ cfu/ml at baseline to $0.61x10^8$ cfu/ml after 1 year ($p=0.004$) in the CHIMRT group.

Table 1. Demographic data of the 82 included patients per treatment group.

Variable	Category	SURG group n=29	IMRT group n=26	CHIMRT group n=27
Age, years	Median (IQR)	60 (54-64)	63 (58-69)	58 (50-62)
Gender	Male / Female	16 / 13	14 / 12	18 / 9
Tumor site	Oral cavity	29 (100%)	17 (65%)	9 (33%)
	Oropharynx	0	9 (35%)	18 (67%)
TNM-classification	T1N0M0	18	5	0
	T1N1M0	2	0	3
	T1N2bM0	0	1	1
	T2N0M0	5	2	0
	T2N1M0	2	1	2
	T2N2bM0	0	3	5
	T2N2cM0	0	0	3
	T2N3M0	0	1	0
	T3N0M0	0	2	3
	T3N2bM0	0	1	0
	T4N0M0	0	3	2
	T4N1M0	0	1	0
	T4N2bM0	0	2	4
	T4N2cM0	0	2	4
	Not reported	2	2	0
Wound closure	Primary	13 (45%)	5 (19%)	4 (15%)
	Skin graft/flap	16 (55%)	10 (38%)	6 (22%)
Self-reported smoking	Yes / In the past	11 / 9 / 8 / 1	9 / 9 / 8	7 / 9 / 11
	No / Not reported			
Alcohol consumption	Yes / No / Not reported	23 / 5 / 1	18 / 8 / 0	23 / 4 / 0
Cumulative IMRT dose	Median (IQR)	NA	66(66-70)	
Primary IMRT		NA	11 (42%)	17 (63%)
Post-operative IMRT		NA	15 (58%)	10 (37%)
Chemotherapy type	Carboplatin/ 5-FU	NA	NA	18 (67%)
	Cisplatin	NA	NA	7 (26%)
	Cetuximab	NA	NA	2 (7%)

NA= not applicable
IQR= inter quartile range
SURG= surgery
IMRT= intensity modulated radiation therapy
CHIMRT= intensity modulated radiation therapy with chemotherapy

Oral lavage total bacterial counts

No significant differences were found between or within groups for total bacterial counts from the oral lavage at the various time points.

Prevalence and proportion of oral microorganisms within the groups

The prevalence and proportion of oral microorganisms in subgingival biofilm samples and oral lavage are shown per treatment group in Figures 1 and 2. The prevalence of periodontal bacterial species in SURG patients tended to decrease at 6 and 12 months, but was only statistically significant for *T. forsythia* (P=0.046).

In the IMRT-group, the prevalence of several periodontal bacterial species, notably *A. actinomycetemcomitans, P. gingivalis, P. intermedia, T. forsythia, P. micra, F. nucleatum* and *C. rectus*, decreased during follow-up with a prominent decrease after baseline and before IMRT (Fig 1B). In contrast, the prevalence of staphylococci increased. In the oral lavage of these patients, the prevalence of *S. mutans* tended to decrease while an increase in prevalence was observed for enteric rods and *Candida* species. Similar changes in prevalence were observed in the CHIMRT patients (Fig 1C).

The prevalence of *P. micra*, *F. nucleatum* and lactobacilli was high in all treatment groups. A drop in prevalence over time was observed in IMRT and CHIMRT patients for *P. gingivalis*, *P. intermedia*, *T. forsythia*, *S. mutans* and *Actinomyces* species.

Proportions of *P. gingivalis*, *P. micra, F. nucleatum* and *C. rectus* were high in all treatment groups. Proportions of enteric rods and *C. albicans* were low. The trends in the prevalence and proportion of microorganisms were comparable in the IMRT and CHIMRT group, while the SURG group showed a different pattern.

Differences between the treatment groups at baseline

The prevalence of lactobacilli at baseline was significantly lower in the IMRT group compared to the CHIMRT group and SURG group (p=0.037; Fig. 1), while the prevalence of *C.albicans* was lower in the SURG group (p=0.043) than in the IMRT and CHIMRT groups (Fig. 1).

Differences between the treatment groups at 6 months follow-up

At 6 months, the prevalence of *Actinomyces* species (p=0.028) and *P. intermedia* (p=0.031) was significantly higher in the SURG group than in the IMRT and CHIMRT groups, and the prevalence of *C. albicans* (p=0.002) was lower in the SURG group compared to the other 2 groups (Figures 1 and 2).

Differences between the treatment groups after 1 year of follow-up

At 1 year follow-up, the prevalence (p=0.001) and proportion (p=0.025) of *C. albicans* were both significantly higher in IMRT and CHIMRT patients compared to SURG patients; the prevalence of *T. forsythia* (p=0.026) and *P. intermedia* (p=0.015) was higher in SURG patients compared to IMRT and CHIMRT patients (Figures 1 and 2).

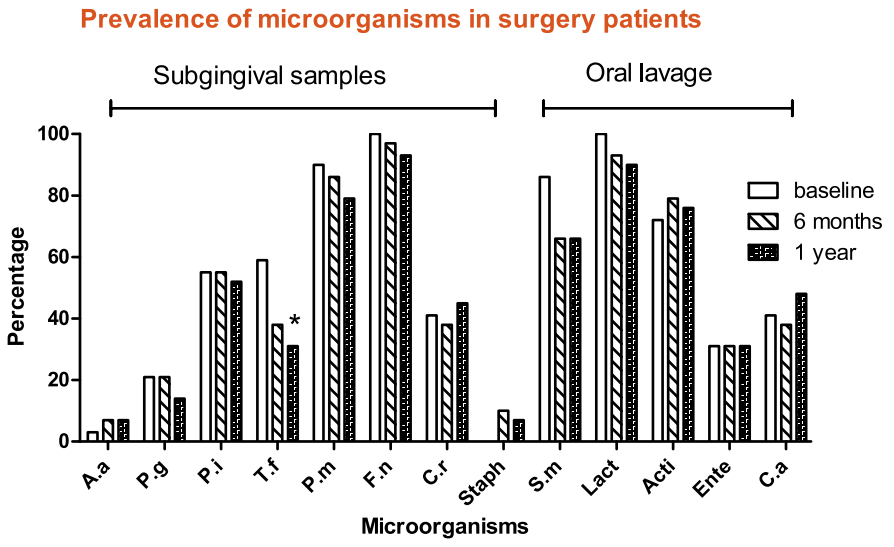

Figure 1A. Bar chart showing the prevalence of microorganisms cultured from subgingival biofilm samples (A.a. up to Staph) and oral lavages (S.m. up to C.a) at baseline, after 6 months and after 1 year of follow-up in surgery patients. A.a= *Aggregatibacter actinomycetemcomitans; P.g= Porphyromonas gingivalis; P.i= Prevotella intermedia; T.f= Tannerella forsythia; P.m= Parvim onas micra; F.n= Fusobacterium nucleatum; C.r= Campylobacter rectus; S.m= Streptococcus mutans; Lact=* lactobacilli; *Acti= Actinomyces* species; *Ente= Enteric rods and C.a= Candida albicans.*
*= significant difference between baseline and 1 year follow-up (p=0.046) for *T. forsythia*.

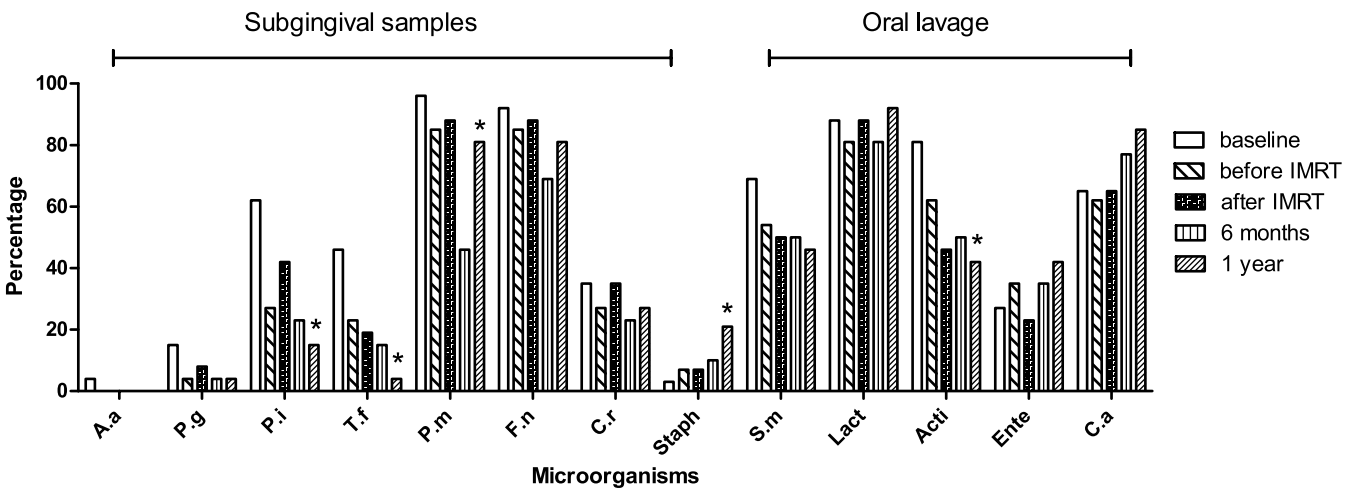

Figure 1B. Bar chart showing the prevalence of microorganisms cultured from subgingival biofilm samples (A.a. up to Staph) and oral lavages (S.m. up to C.a) at baseline, before IMRT, 6 weeks after IMRT, after 6 months and after 1 year of follow-up in IMRT patients. A.a= *Aggregatibacter actinomycetemcomitans; P.g= Porphyromonas gingivalis; P.i= Prevotella intermedia; T.f= Tannerella forsythia; P.m= Parvimonas micra; F.n= Fusobacterium nucleatum; C.r= Campylobacter rectus; S.m= Streptococcus mutans; Lact=* lactobacilli; *Acti= Actinomyces* species; *Ente= Enterics and C.a= Candida albicans.*
*= significant difference between baseline and 1 year follow-up for *P. intermedia* (p=0.001), *T. forsythia* (p=0.001), *P.micra* (p=0.046), staphylococci (p=0.025) and *Actinomyces* species (p=0.012).

Prevalence of microorganisms in CHIMRT patients

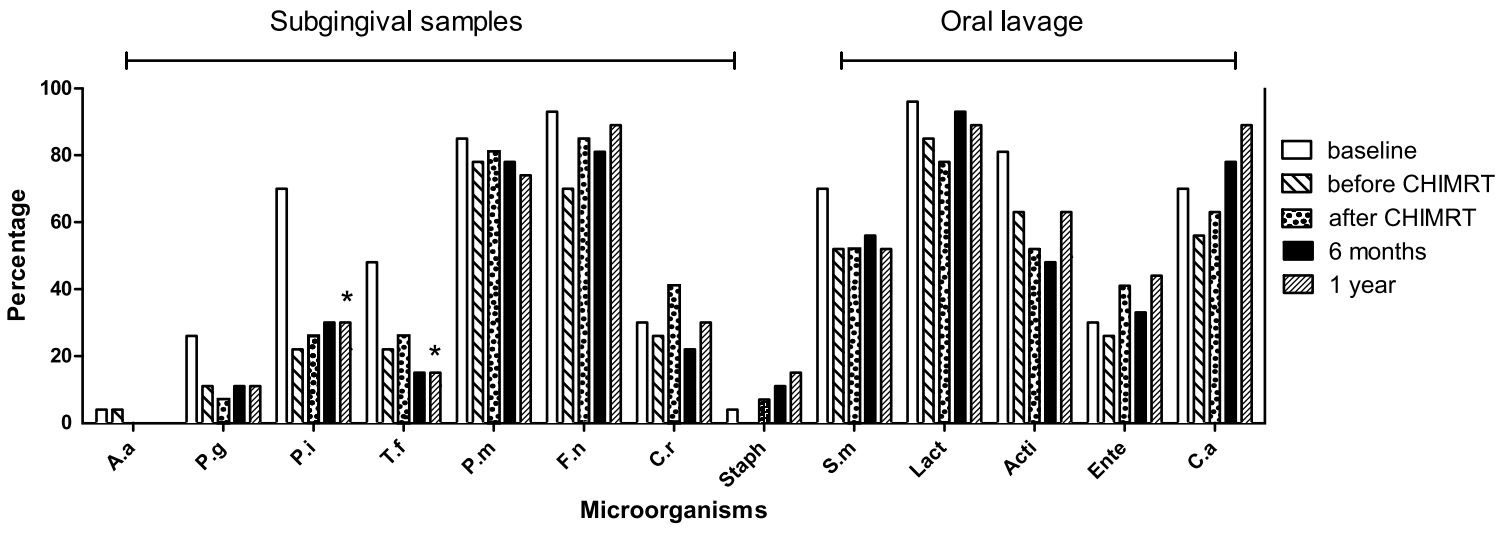

Figure 1C. Bar chart showing the prevalence of microorganisms cultured from subgingival biofilm samples (A.a. up to Staph) and oral lavages (S.m. up to C.a) at baseline, before CHIMRT, after 6 weeks CHIMRT after 6 months and after 1 year of follow-up in chemoradiation patients. A.a= *Aggregatibacter actinomycetemcomitans; P.g= Porphyromonas gingivalis; P.i= Prevotella intermedia; T.f= Tannerella forsythia; P.m= Parvimonas micra; F.n= Fusobacterium nucleatum; C.r= Campylobacter rectus; S.m= Streptococcus mutans; Lact=* lactobacilli*; Acti= Actinomyces* species; *Ente= Enteric rods and C.a= Candida albicans.*
*= significant difference between baseline and 1 year follow-up for *P. intermedia* (p=0.005) and *T. forsythia* (p=0.020).

Mean % of microorganisms in positive cultured surgery patients

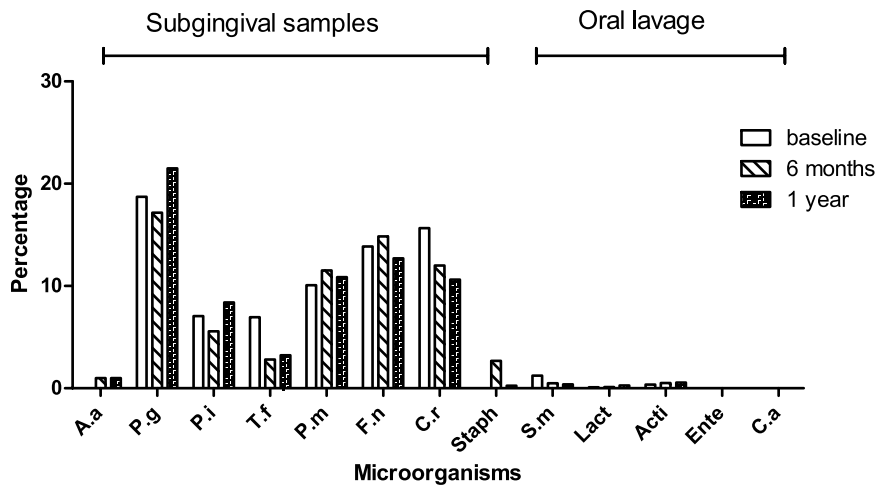

Figure 2A. Bar chart showing the mean percentage of microorganisms in culture positive surgery patients cultured from subgingival biofilm samples (A.a. up to Staph) and oral lavages (S.m. up to C.a) at baseline, after 6 months and after 1 year of follow-up. A.a= *Aggregatibacter actinomycetemcomitans; P.g= Porphyromonas gingivalis; P.i= Prevotella intermedia; T.f= Tannerella forsythia; P.m= Parvimonas micra; F.n= Fusobacterium nucleatum; C.r= Campylobacter rectus; S.m= Streptococcus mutans; Lact=* lactobacilli*; Acti= Actinomyces* species; *Ente= Enterics and C.a= Candida albicans.* Mean proportions for Enteric rods and *C.albicans* were close to zero; due to scaling they are not visible on this chart.

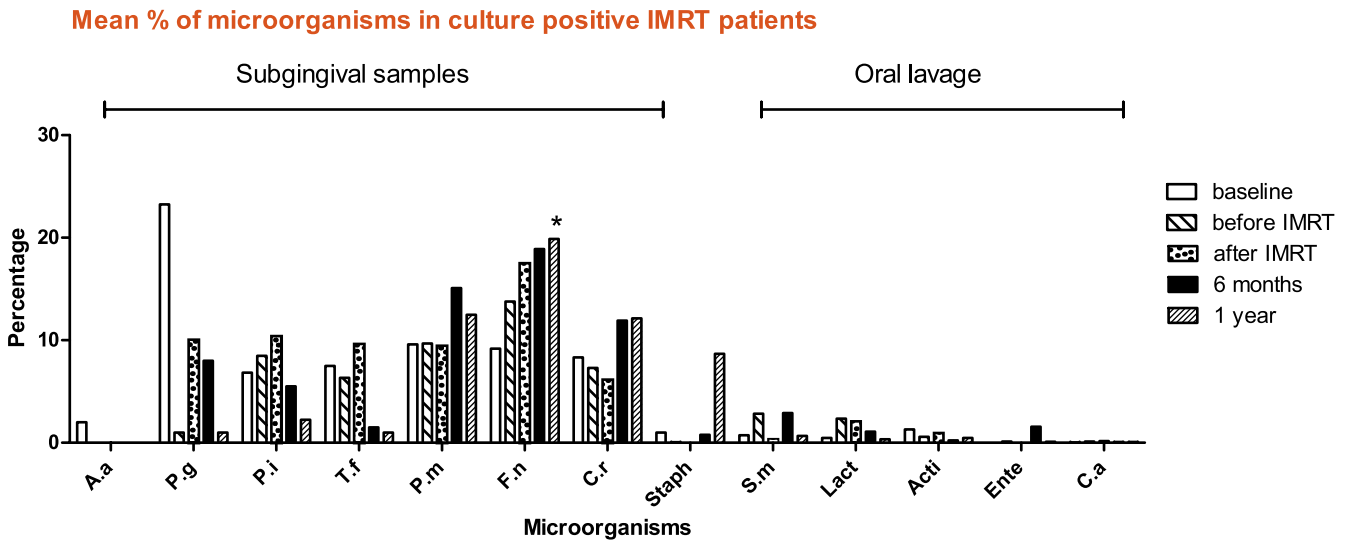

Figure 2B. Bar chart showing the mean percentage of microorganisms in culture positive IMRT patients cultured from subgingival biofilm samples (A.a. up to Staph) and oral lavages (S.m. up to C.a) at baseline, before IMRT, after 6 weeks IMRT, after 6 months and after 1 year. A.a= *Aggregatibacter actinomycetemcomitans; P.g= Porphyromonas gingivalis; P.i= Prevotella intermedia; T.f= Tannerella forsythia; P.m= Parvimonas micra; F.n= Fusobacterium nucleatum; C.r= Campylobacter rectus; S.m= Streptococcus mutans; Lact=* lactobacilli*; Acti= Actinomyces* species; *Ente= Enteric rods and C.a= Candida albicans.*
*= significant difference between baseline and 1 year follow-up for *F.nucleatum* (p=0.015). Mean proportions for Enteric rods and *C.albicans* were close to zero; due to scaling they are hardly visible on this chart.

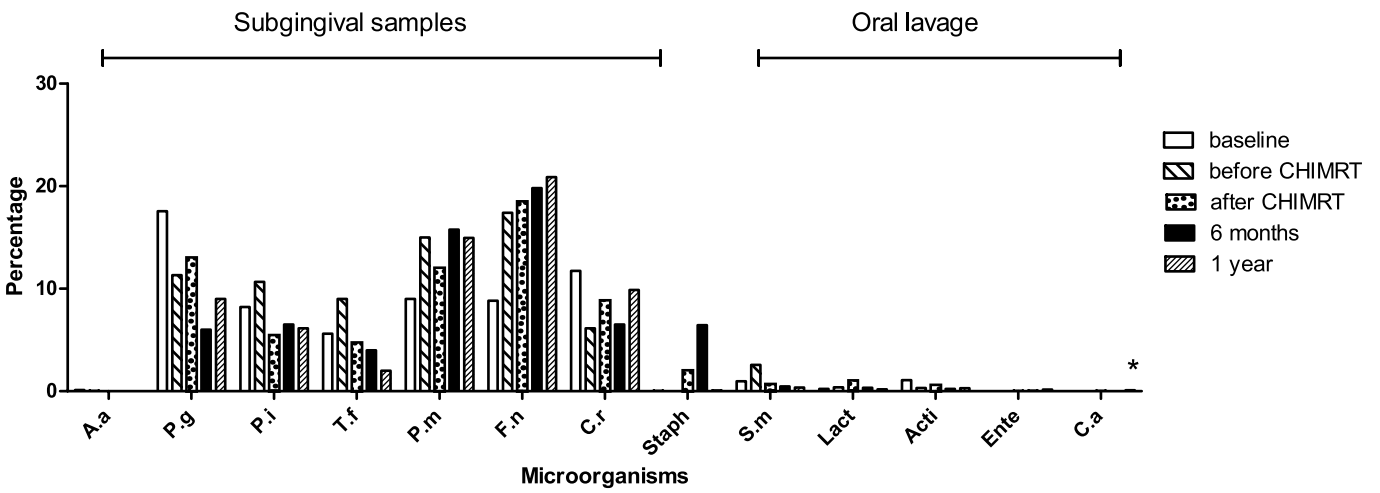

Figure 2C. Bar chart showing the mean percentage of microorganisms in culture positive CHIMRT patients cultured from subgingival biofilm samples (A.a. up to Staph) and oral lavages (S.m. up to C.a) at baseline, before CHIMRT, after 6 weeks CHIMRT, after 6 months and after 1 year of follow-up. A.a= *Aggregatibacter actinomycetemcomitans; P.g= Porphyromonas gingivalis; P.i= Prevotella intermedia; T.f= Tannerella forsythia; P.m= Parvimonas micra; F.n= Fusobacterium nucleatum; C.r= Campylobacter rectus; S.m= Streptococcus mutans; Lact= lactobacilli; Acti= Actinomyces* species; *Ente= Enteric rods and C.a= Candida albicans*.*= significant difference between baseline and 1 year follow-up for *C. albicans* (p=0.019). Mean proportions for Enteric rods and *C.albicans* were close to zero; due to scaling they are not visible on this chart.

Salivary flow rate

Unstimulated and stimulated salivary flow rate decreased significantly in IMRT and CHIMRT patients (Table 2). Notably, hyposalivation was ascertained at baseline in 2 SURG patients, 4 IMRT patients and 6 CHIMRT patients.

Relation oral microflora and salivary flow rate

Patients who tested positive for *C.albicans* at baseline, 6 months and 1 year had a significantly lower unstimulated saliva flow at all three time points than patients who tested negative (p=0.018, p<0.001 and p=0.027, respectively).

Other factors of influence on oral microflora composition

Plaque and bleeding score

Plaque and bleeding scores did not differ between treatment groups at baseline, 6 months and 1 year. In the total group (n=82), baseline median plaque score was 50% (IQR 23-70%) and median bleeding score was 40% (IQR 20-60%). After one year, median scores declined to 25% for plaque and 10% for bleeding (p<0.001 and p=0.001, respectively). In the SURG group, baseline median plaque score was 50% (IQR 20-68%) and median bleeding score was 50% (IQR 20-75%). After one year, median scores declined to 20% for both plaque and bleeding (p<0.001 and p=0.001, respectively). In the IMRT group, baseline median plaque score was 50% (IQR 20-71%) and median bleeding score 30% (IQR 10-50%). After one year, median scores declined to 30% for plaque and 20% for bleeding (p=0.085 and p=0.840, respectively). In the CHIMRT group, baseline median plaque score was 50% (IQR 25-80%) and median bleeding score 40% (IQR 20-70%). After one year, median scores declined to 20% for both plaque and bleeding (p=0.001 and p=0.001, respectively).

PISA

The baseline PISA score was significantly different between treatment groups, with lower values in the IMRT group (mean 341mm^2) compared to the SURG and CHIMRT groups (mean 729 and 733mm^2, respectively). Baseline PISA scores were not associated with baseline prevalence of the cultured microorganisms.

Smoking

The number of patients who smoked did not differ between the treatment groups at baseline and after 1 year (Table 1). In the total group (n=82), the number of smokers had decreased from 27 at baseline to 17 after 1 year (p=0.005). Baseline prevalence of *T. forsythia* was significantly higher in smokers than in non-smokers (p=0.022). The number of smokers decreased within all groups comparing baseline and 1 year; in the SURG group from 11 to 9 (p=0.480), in the IMRT group from 8 to 4 (p=0.046) and in the CHIMRT group from 8 to 4 (p=0.083).

Table 2. Mean and SD of salivary flow rate per treatment group.

Treatment groups	Baseline UWS flow ml/min mean (SD)	6 months UWS flow ml/min mean (SD)	1 year UWS flow ml/min mean (SD)	Baseline SWS flow ml/min mean (SD)	6 months SWS flow ml/min mean (SD)	1 year SWS flow ml/min mean (SD)
SURG group	0.53 (0.46)	0.68 (0.72)	0.76 (0.64)	1.55 (0.96)	1.55 (1.0)	1.37 (0.98)
IMRT group	0.57 (0.50)	0.20[a] (0.18)	0.25[b] (0.18)	1.05 (0.86)	0.51 (0.40)	0.62[c] (0.53)
CHIMRT group	0.38 (0.33)	0.22[d] (0.21)	0.29[e] (0.32)	1.04 (0.85)	0.50[f] (0.51)	0.60[g] (0.66)

Significant differences were found after 6 months of follow-up between the 3 treatment groups for unstimulated (p<0.001) and stimulated salivary flow (p<0.001). After 1 year of follow-up, significant differences were found between the 3 treatment groups for unstimulated (p<0.001) and stimulated salivary flow (p=0.003).
Significant difference compared to baseline data with: [a](p=0.002), [b](p=0.015), [c](p=0.045), [d](p=0.005) [e](p=0.032), [f](p=0.001), [g](p=0.006)
SD= standard deviation, SURG=surgery, IMRT= intensity modulated radiation therapy, CHIMRT= intensity modulated radiation therapy with chemotherapy, UWS= unstimulated whole saliva, SWS=stimulated whole saliva.

Oral foci

The number of patients with oral foci of infection at dental screening was highest in the SURG group (93%) compared to 73% in the IMRT group and 82% in the CHIMRT group (p=0.139).

The prevalence of *F. nucleatum* at dental screening was significantly higher amongst patients with oral foci of infection, mainly periodontal disease, compared to patients without oral foci of infection (99% versus 85%, p=0.015). The prevalence of *F. nucleatum* was still significantly higher amongst patients with oral foci of infection at 6 months (p=0.005) but no significant difference was found between patients with and without oral foci of infection after 1 year.

Discussion

The trends in changes in prevalence and proportions of microorganisms were comparable in the IMRT and CHIMRT groups, whereas the SURG group showed a different pattern. In the IMRT and CHIMRT groups, increased prevalence of opportunistic pathogens, such as enteric rods, staphylococci and *Candida* species, was observed. In these groups, elimination of oral foci decreased the frequency of detection of major pathogens such as *P. gingivalis, T. forsythia* and *S. mutans*. The oral side effects of chemotherapy are essentially temporary and reversible [28]. Apparently, IMRT/CHIMRT has a similar long-term effect on microbial composition as 3D-CRT.

Comparison of our findings with previous studies

The results of this study showed an increased prevalence of opportunistic pathogens such as enteric rods, staphylococci and *Candida* species, which are associated to underlying disease. In the 1960s, Johanson et al. (1969) showed that illness causes a shift of microbial populations of the throat towards gram-negative bacilli [29]. After 3D-CRT, increased prevalence of both of *C. albicans* [9,11,15,30] and staphylococci [30] have been described. However, to our knowledge, no studies have shown such effects in IMRT patients. After IMRT it could be expected that different changes in oral microflora would be seen due to the less reduced salivary flow compared to 3D-CRT [31-33], We found a 56% reduction of unstimulated salivary flow in the IMRT group during 1 year of follow-up and a 24% reduction in the CHIMRT group. Although it was difficult to find comparable studies in terms of treatment group and outcomes, a 3D-CRT study showed a much more profound reduction (93%) of unstimulated salivary flow rate after 1 year of follow-up in patients with oropharynx carcinoma treated with 3D-CRT or chemoradiation [34]. Even though we did find less reduced salivary flow after IMRT, our study showed that the prevalence of opportunistic pathogens still increases after IMRT to levels similar to those reported after 3D-CRT [13-15].

The total bacterial counts decreased over time in all groups. It is known that patients with oral squamous cell carcinoma have a significantly larger median number of cfu/ml saliva than healthy controls [35]. Treatment of the cancer probably led to the decrease in total bacterial counts in all treatment groups (SURG, IMRT and CHIMRT). Also, oral hygiene improved substantially in our cohort, which could also explain this effect.

Particularly remarkable is the decline in prevalence over time in all 3 treatment groups for *S. mutans* and in the SURG and CHIMRT group for lactobacilli. These findings are in contrast with literature reporting high numbers and proportions of acidogenic microorganisms after 3D-CRT [13,15,30,36]. However, after IMRT a smaller reduction in salivary flow was reported [7], which might explain the lower numbers of acidogenic microorganism found in our study, as the oral cavity is probably less acidic. Another explanation could be that only few patients in this study had active caries at baseline and/or during follow-up. Patients were subjected to an intensive oral care protocol and their oral hygiene improved substantially during follow-up.

After full-mouth tooth extraction, de Waal et al. reported a reduction of A. *actinomycetemcomitans, P. gingivalis, P. intermedia, T. forsythia, P. micra, F. nucleatum,* and *C. rectus* after 4 weeks and 3 months [37]. Similarly, we observed a decrease of the same periodontal pathogens in the IMRT and CHIMRT groups during follow-up with a profound decrease after 'baseline' and 'before RT'. In the period between 'baseline' and 'before RT', patients' teeth that were classified as oral foci of infection were removed at least 10 days before the onset of IMRT or CHIMRT. Our results demonstrate the almost immediate effect on oral microflora after the elimination of oral foci of infection (mainly periodontally affected teeth).

We found a significantly higher baseline prevalence of *T. forsythia* in smokers than in non-smokers. This was an expected outcome since *T. forsythia* is associated with smoking [38]. In the SURG group, we found a significant decrease in prevalence of *T. forsythia* over time. Although no significant decrease of the number of smokers in the SURG group was found, 50% of smokers in the SURG group did quit smoking, which may have contributed to the significant decrease in prevalence of *T. forsythia.* Our institution supports HNC patients in their efforts to quit smoking as this improves their survival and treatment outcomes [39].

Implications

Our study reported on the long term effects of IMRT on oral microflora. Few comparable studies are available, primarily because this treatment modality is relatively new. Regarding the prevalence of opportunistic pathogens after IMRT and CHIMRT, the results after IMRT were comparable to those after 3D-CRT. This was unexpected, since IMRT causes a smaller reduction in salivary flow and has presumed positive effects on oral tissues and microflora. Our study showed that despite the less reduced salivary flow, opportunistic pathogens still increase.

Conclusion

Different treatments in HNC patients result in different changes in the oral microflora. Opportunistic pathogens such as staphylococci, enteric rods and *Candida* species tend to increase in prevalence after IMRT with or without chemotherapy, but not after surgical intervention.

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Chapter 5

Patients with periodontal disease before intensity modulated radiation therapy are prone to develop bone healing problems: a 2-year prospective follow-up study

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Submitted

Abstract

Background and Purpose: Intensity modulated radiation therapy (IMRT) has changed radiation treatment of head and neck cancer (HNC). However, it is still unclear if and how IMRT changes oral morbidity outcomes. In this prospective study we assessed the efficacy of reducing post-radiotherapy sequelae of IMRT by means of pre-radiation dental screening and eliminating oral foci of infection.

Materials and Methods: All consecutive dentate patients >18 years, diagnosed with primary oral or oropharyngeal carcinoma, referred for pre-treatment dental screening between May 2011 and May 2013, were included and followed for 2 years. Patients were treated with IMRT or IMRT with chemotherapy (CHIMRT). Dental screening data, demographic data and data on oral sequelae during follow-up were recorded.

Results: Oral foci of infection were found in 44/56 (79%) patients, consisting predominantly of periodontal breakdown. Bone healing problems after radiotherapy occurred more often in patients with periodontal pockets ≥6 mm at baseline ($p<0.05$). Osteoradionecrosis developed in 4/56 patients (7%) during follow-up.

Conclusions: Patients with periodontal disease before IMRT/CHIMRT are prone to develop bone healing problems during post-radiotherapy follow-up.

Introduction

HNC patients treated by radiotherapy are at risk of developing severe oral sequelae for their remaining lifespan. Periodontal disease, radiation-induced xerostomia and radiation-related caries may require dental extractions and consequently result in an increased risk of developing osteoradionecrosis (ORN) of the jaw [1-3]. ORN is radiation-induced destruction of the bone. It is difficult to treat, is not self-limiting, and may require extensive invasive surgery and/or adjuvant treatment with hyperbaric oxygen. Hypovascularity and hypocellularity of irradiated bone and soft tissues are considered the predominant underlying patho-physiologic mechanisms, which have low reparative ability [4,5]. The majority of ORN cases develop within 3 years after radiotherapy [6].

Risk factors for developing ORN include post-irradiation extractions [1], periodontal loss/periodontitis [2], oral surgical interventions [7] and dental status [8]. To prevent such oral morbidity after radiotherapy, in particular ORN, pre-radiation dental screening is commonly performed to locate and eliminate oral foci of infection, although the efficacy of these interventions is unclear [3]. An oral focus is defined as a pathologic process in the oral cavity that does not cause major problems in healthy individuals, but may lead to severe local or systemic inflammation under certain circumstances [1,9].

During the last decade, treatment of HNC has changed substantially, particularly due to the introduction of intensity modulated radiation therapy (IMRT) and concomitant chemoradiation [10]. The effects of IMRT on the oral tissues and jaw bone in particular are not yet clearly understood. IMRT results in less xerostomia due to sparing of the parotid and/or submandibular glands [11]. However, dose redistribution resulting from salivary gland sparing may lead to higher doses to the other tissues in the radiation field, in particular to the mucosa of the oral cavity, which can result in “beam path toxicities” [12]. These potentially higher doses to jaw bone and oral cavity entail a higher risk of developing ORN during post-radiotherapy follow-up [5]. However, current pre-radiation dental screening protocols are based on conventional radiotherapy and require an update to take account of the effects of IMRT. We therefore conducted a prospective 2-year follow-up cohort study to assess the efficacy of pre-radiation dental screening and elimination of oral foci of infection in HNC patients treated with IMRT. Results were compared to those of a historical control group treated with conventional radiotherapy [2].

Methods

Patients

All consecutive dentate or partially dentate patients >18 years, diagnosed with primary oral or oropharyngeal squamous cell carcinoma, who were referred to the University Medical Center Groningen (UMCG), the Netherlands, for pre-treatment

dental screening between May 2011 and May 2013 were included in this study if definitive radiotherapy to the head and neck region was part of the treatment plan. Patients who had undergone previous oncologic treatment (surgery and/or radiotherapy and/or chemotherapy) to the head and neck region were excluded as well as patients with unknown primary or parotid gland tumors. A standardized follow-up of 2 years post-oncologic treatment related to oral and dental morbidity was completed (JMS). Written informed consent was obtained from all patients. The medical ethical committee of the UMCG approved the study protocol (METC 2012/091).

Dental screening

All patients were evaluated before their oncologic treatment as part of routine clinical practice by means of oral and dental screening, including radiographic examination [13]. Plaque and bleeding scores were assessed as a percentage of the total number of sites with plaque respectively bleeding on probing. To quantify periodontal disease, the periodontal inflamed surface area (PISA) was used [14]. Patients were asked about their smoking and drinking habits. Self-reported smoking options were 'current smoker', 'past smoker', or 'never smoked' and self-reported alcohol consumption options were 'never drink alcohol' or 'drink alcohol'.

All data obtained at baseline and follow-up visits (Table 1) were collected in pre-determined order and recorded using a standardized study form designed for this study.

IMRT

All included patients were subjected to definitive primary or postoperative IMRT or definitive primary or postoperative chemoradiation (CHIMRT). IMRT was given according to standard protocol as previously described [2]. Chemotherapy was given concurrently with fractionated IMRT and consisted of Carboplatin on day 1 (300–350 mg/m^2 in 30 min intravenously) and 5-fluorouracil (5-FU) from day 1 to 4 by continuous infusion (600 mg/m^2/24 h), consisting of 3 courses given with an interval of 3 weeks. Postoperative chemotherapy consisted of 6x50 mg Cisplatin weekly. When chemotherapy was considered to be infeasible, patients were treated with cetuximab using a loading dose of 400 mg/m^2 one week prior to radiotherapy and a weekly dose of 250 mg/m^2 during radiotherapy.

Treatment of oral foci of infection

Before onset of IMRT or CHIMRT, oral foci of infection were eliminated (Table 2), if teeth related to the foci were within the radiation field or likely to be within the radiation field receiving a cumulative dose >40Gy. An oral focus of infection was defined as [3]:

- deep caries in which excavation may lead to pulpal exposure;
- active periodontal disease with pockets ≥6mm, furcation ≥grade 1, mobility >grade 1, gingival recession ≥6mm and especially a combination of these periodontal problems;
- non-restorable teeth with large restorations, especially those extending beyond the gum line or with root caries, or those with severe erosion or abrasion;
- periapical granuloma and avital teeth;
- impacted, partially impacted or partially erupted teeth not fully covered by bone or showing radiolucency;
- cysts and other radiographic abnormalities.

Dental pathology not defined as an oral focus of infection was treated according to professional standards. Before the onset of IMRT or CHIMRT, patients were seen by a dental hygienist for dental prophylaxis and oral hygiene instructions.

Oral care during radiotherapy

During IMRT and CHIMRT, patients were seen daily (Monday to Friday) by a dental hygienist for spraying the oral cavity with saline according to standard protocol [15]. Instructions were given to continue normal daily oral care (tooth brushing and/or interdental cleaning) as long as possible, and to rinse the mouth with salt-baking soda solution at home, 8-10 times per day [13]. Dentate IMRT and CHIMRT patients received custom-made fluoride trays and were prescribed a neutral 1% sodium fluoride gel to be used every second day [13,16,17].

Follow-up

Regular oncology follow-up visits to the OMS, dental hygienist and/or hospital dentist were combined with visits to the researcher (JMS) to collect study data (Table 1). Dental follow-up by the dental hygienist and hospital dentist is standard for IMRT and CHIMRT patients every 3-6 months, depending on the patient's needs, during at least 5 years after treatment. Oral sequelae during follow-up were recorded, including caries, periodontal disease, restorative problems, bone healing problems and ORN. According to the prevailing definition, ORN is an area of exposed devitalized irradiated bone that fails to heal over a period of 3 months in the absence of local neoplastic disease [4,18-20]. If oral sequelae occurred during follow-up, and an irradiated patient needed treatment, radiation fields were always verified with the department of Radiation Oncology. Antibiotic prophylaxis was given in case of surgical intervention and, if the dose in the specific region where treatment was needed was >40Gy, hyperbaric oxygen therapy was considered depending on patient factors, such as smoking, general health and complexity of the removal of the affected teeth. If oral sequelae occurred during follow-up and if they were within the radiation field (≥40Gy), all efforts were made to prevent tooth extraction. All data (dental screening and follow-up visits) were recorded using the standardized study form. Dental hygienists were instructed by the researcher on how to use the study form.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 22.0 for Windows. Values of $p<0.05$

Table 1. Overview of data collection in chronological order

Data collection and sampling	Dental screening	Before onset of IMRT or CHIMRT	6 weeks after IMRT or CHIMRT	Every 6 months until end of follow-up
Panoramic X-ray	X			X
General health and medication	X	X	X	X
Alcohol/Tobacco	X	X	X	X
Oral examination	X	X	X	X
Periodontal examination incl. plaque and bleeding score	X			X

IMRT= intensity modulated radiation therapy; CHIMRT= IMRT with chemotherapy

were considered significant. Testing for significance was done using Chi-square tests for binary data (developing ORN, having bone healing problems) and Kruskal-Wallis tests for quantitative data (PISA scores). The Wilcoxon signed rank test was used for comparing baseline PISA scores with follow-up data.

Results

Demographics

Between May 2011 and May 2013, 56 patients met the inclusion criteria (Fig. 1). Follow-up ranged from 11 to 24 months, with a median of 24 months (Fig. 2). Demographics, clinical characteristics and baseline dental data of all patients are summarized in Table 3.

After dental screening and pre-radiation treatment of oral foci, 5 patients needed a full mouth clearance (Fig. 1). The results on oral sequelae during follow-up are therefore based on the 51 remaining dentate patients. The results on dental screening and bone healing problems are based on the original 56 patients.

Dental screening and treatment of oral foci of infection

Out of 56 patients, 44 (79%) had 1 or more oral foci at dental screening (Fig. 3). The periodontal condition at baseline was healthy (no pockets) in 3 patients, pockets of 4-5mm in 25 patients and pockets ≥6 mm in 28 patients. This means that 53 out of 56 patients (95%) had periodontal disease to some extent at baseline.

Pre-radiotherapy dental extractions were needed in 44 patients, including full mouth clearance in 5 patients (11%). A median of 7 teeth were extracted per patient (IQR [2-10]). One patient had a dental cyst (premolar region mandible) that was surgically removed. After focus elimination, the periodontal condition of the 51 dentate patients was healthy in 3 patients, while 48 patients had pockets of 4-5 mm.

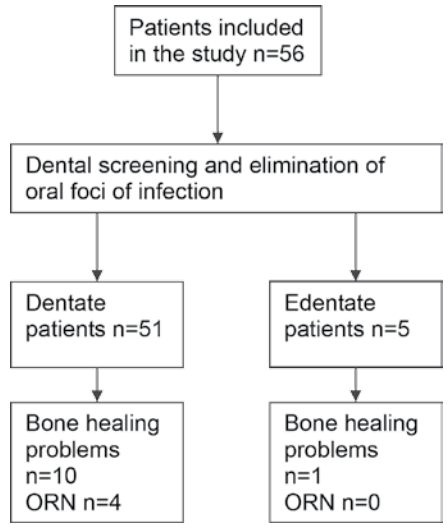

Figure 1. Flow chart of included patients showing dentate and edentate patients.

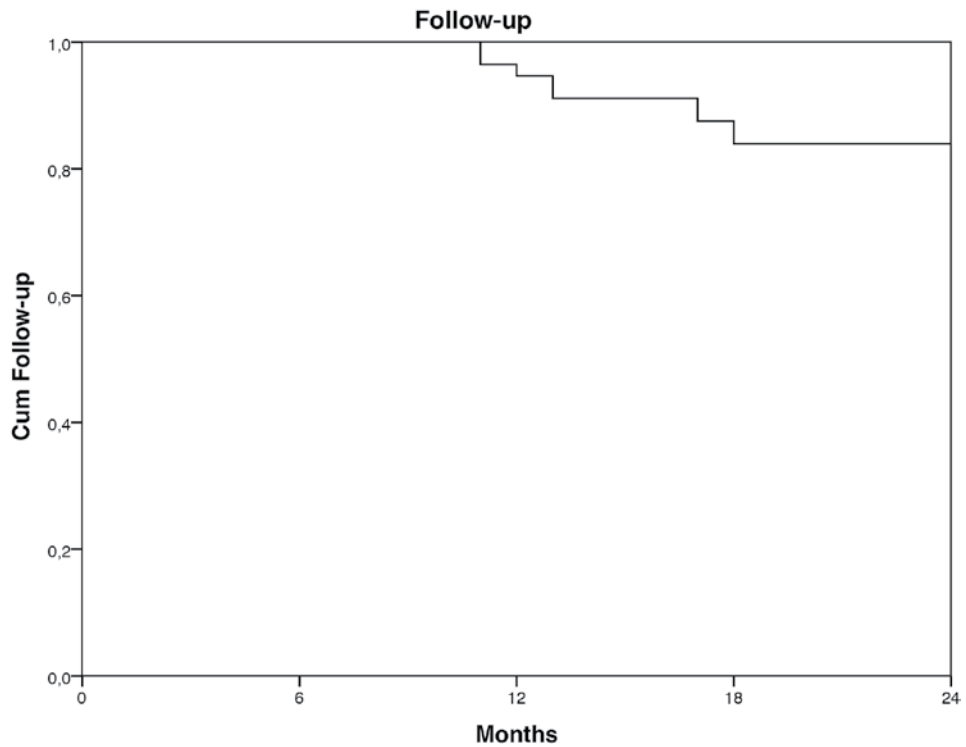

Figure 2. Kaplan Meier plot of follow-up in months.
Nine patients dropped out before the end of the study: 2 were lost to follow-up, 2 patients died and 5 patients were diagnosed with metastatic or recurrent disease and declined health care.

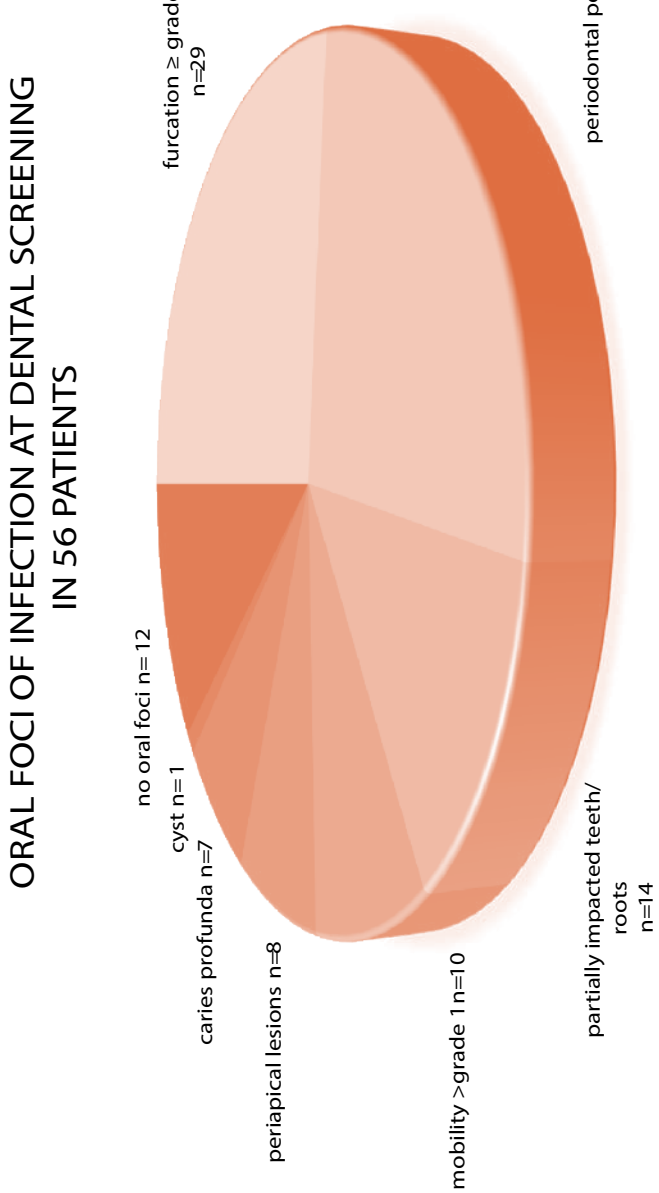

Figure 3. Oral foci of infection were found in 44 out of 56 patients. Since patients were occasionally diagnosed with more than one oral focus, the sum of the numbers exceeds 44. Patients had 1 to 6 oral foci with a mean of 2.3 foci per patient (SD=1.1).

Oral sequelae during follow-up

Oral hygiene and fluoride prophylaxis

All 51 dentate patients were instructed to brush their teeth daily and to use fluoride gel every other day during follow-up, occasionally with the exception of a short period during or after radiation related to radiotherapy-related sensitivity of the gums or oral mucosa.

Comparing baseline and 2 years of follow-up, plaque and bleeding scores decreased significantly. Plaque scores were reduced from a median of 50% to 30% (p=0.016) and bleeding scores from 30% to 10% (p=0.027).

Post-radiotherapy periodontal health

Post-radiotherapy, 12 out of 51 dentate patients (24%) had progression of periodontal pocket depth (4-5mm pockets deepened) and/or development of new periodontal pockets (4mm or deeper measured on a site that was ≤3mm before) (24%). Eight out of these 12 patients had teeth removed after dental screening before radiation because of pockets ≥6mm, and all of them had remaining pockets of 4-5mm (not considered as oral foci) before the onset of radiotherapy.

PISA scores decreased significantly during follow-up when baseline PISA scores (Table 3) were compared with PISA scores at 6 months (median 225; IQR[139-08]; p=0.006) and 2 years after IMRT (median 149; IQR[77-357]; p=0.003). This was probably due to the elimination of oral foci of infection and improved oral hygiene.

Post-radiotherapy tooth extractions

Six patients (12%) needed one to three post-radiotherapy tooth extractions because of caries profunda (n=4) or periodontal disease (n=2).

Post-radiotherapy dental caries

Out of 51 dentate patients, 13 (25%) developed 1 or more carious lesions.

Post-radiotherapy periapical pathosis

Out of 51 patients, 3 patients (6%) developed caries profunda with periapical pathosis during follow-up, discovered on radiographs or from symptoms. Endodontic treatment or tooth extraction was performed.

Post-radiotherapy bone healing problems and ORN

Bone healing problems were observed in 11 out of 56 patients (20%): 6 patients were diagnosed with delayed wound healing after pre-radiotherapy (n=5) or post-radiotherapy (n=1) tooth extraction, 1 with lingual mandibular sequestration (unrelated to tooth extraction) and 4 with ORN (more details below). Of these 11 patients, 1 patient developed bone healing problems after pre-radiotherapy full mouth clearance. The other 10 patients had teeth left after elimination of oral foci and during the 2 years of follow-up.

Of the 28 patients with baseline periodontal pockets ≥6 mm, 6 developed bone healing problems, not yet diagnosed as ORN, during follow-up (21%). An increased risk of bone healing problems was found in patients with periodontal pockets ≥6 mm at baseline compared to patients with pockets <6mm at baseline (p=0.043).

Of the 28 patients with periodontal pockets ≥6 mm at baseline, 2 developed ORN (7%). No increased risk for developing ORN was found in patients with periodontal pockets ≥6 mm at baseline compared to patients with pockets <6mm at baseline (p=1.000).

None of the 3 patients without periodontal pockets at baseline developed bone healing problems or ORN during 2-year follow-up.

Grade I ORN [4] developed in 1 patient, 3 months after completion of postoperative IMRT in an area where a periodontally affected mandibular molar was removed pre-radiotherapy.

Grade II ORN [4] developed in 1 patient, 7 months after postoperative CHIMRT. Due to a restricted mouth opening, scar tissue of the cheek and pain, the patient had problems cleaning the molar in the mandible (right side) after oncologic treatment. Caries developed in the most distal molar and eventually caused pain of endodontic origin. Endodontic treatment was impossible to perform and the molar was extracted post-radiotherapy resulting in a non-healing socket and eventually ORN. This patient was free of oral foci of infection at baseline, but had pockets of 4-5mm at baseline.

Grade III ORN [4] was seen in 2 patients. Idiopathic grade 3 ORN of the angle of the mandible resulting in a pathologic fracture developed in one patient 2 months after CHIMRT had ended. This patient was free of periodontal disease during follow-up. In the other patient, ORN was unrelated to pre- or post-radiotherapy tooth extractions, as it was observed 2 months after postoperative IMRT in the transplanted fibula bone used for reconstruction of the mandible. The patient did have post-RT surgery, however, to remove reconstruction plates. This patient had periodontal pockets 4-5mm at baseline.

Many factors might influence the development of bone healing problems after radiotherapy. Patients with (n=11) and without (n=45) bone healing problems were compared for number of teeth extracted after dental screening (p=0.105), number of teeth at dental screening (p=0.282), T-stage of the tumor (p=0.257), having diabetes (p=0.263), smoking at baseline (p=0.432), drinking alcohol at baseline (p=0.220), baseline plaque (p=0.725) and bleeding score (p=0.384), baseline PISA-score (p=0.076), and having periodontal pockets ≥4mm (p=0.379) or ≥6mm at dental screening (p=0.093).

Table 2. Assessment and treatment of oral foci of infection within or outside the radiation field

Assessed tooth problems	Treatment if cumulative dose >40Gy*	Treatment if cumulative dose <40Gy or outside the radiation portal*
Caries profunda	Tooth extraction	Restoration, if necessary combined with endodontic treatment, or tooth extraction
Periapical pathosis (on radiographs) without symptoms and/or additional problems	In teeth *without* root canal filling: Endodontic treatment and/ or apexification In teeth *with* root canal filling: Endodontic re-treatment, apexification or tooth extraction (needed in case of pre-radiotherapy time limitations)	In teeth *without* root canal filling: Endodontic treatment In teeth *with* root canal filling: Endodontic re-treatment, apexification or tooth extraction Treatment can be postponed until after radiotherapy
Extensive periapical pathosis (on radiographs) combined with periodontal disease, in afunctional teeth or *with symptoms*	Tooth extraction	In teeth *without* root canal filling: Endodontic treatment combined with initial periodontal treatment In teeth *with* root canal filling: Endodontic re-treatment, apexification or tooth extraction depending on the prognosis
Avital pulp *with symptoms* without periapical radiolucency on radiographs	Endodontic treatment or tooth extraction (which might be necessary in case of pre-radiotherapy time limitations)	Endodontic treatment or tooth extraction depending on the prognosis
Avital pulp *without symptoms* and without periapical radiolucency on radiographs	Endodontic treatment or tooth extraction (needed in case of pre-radiotherapy time limitations)	Endodontic treatment (which can be postponed until after radiotherapy)
Periodontal disease with: **Pockets 4-5mm** **Pockets ≥6mm** **Gingival recessions ≥6mm**	Initial periodontal therapy Tooth extraction Tooth extraction	Initial periodontal therapy Initial periodontal therapy Only recession requires no treatment
Impacted teeth or roots fully covered by bone without radiographic abnormalities	No treatment If problems are expected in the future: tooth extraction	No treatment
Impacted teeth or roots *not fully covered* by bone or with radiographic abnormalities (e.g., cysts, apical radiolucency)	Tooth extraction	No treatment or, in case of symptoms, surgical removal Roots with periapical radiolucency might be worth preserving by endodontic treatment and restoration (which can be postponed until after radiotherapy)
Cysts	Surgical removal	Surgical removal
Internal or external root resorption	Tooth extraction	Endodontic treatment or tooth extraction depending on the prognosis

* If an irradiated patient needed treatment, radiation fields were always verified with the department of Radiation Oncology, and depending on the dose in the specific region where treatment was needed, antibiotic prophylaxis was given to the patient

Discussion

This study showed that patients with periodontal disease before IMRT/CHIMRT are prone to develop bone healing problems during post-radiotherapy follow-up. The assessed protocol for elimination of oral foci of infection pre-IMRT was compared to a historical control group treated with conventional radiotherapy [2]; the protocol was equally effective for patients treated with IMRT/CHIMRT. Post-radiotherapy oral and dental morbidity seen in IMRT/CHIMRT patients is comparable to that seen in patients treated with conventional radiotherapy.

The relationship between periodontal disease and bone healing problems is supported by our finding that baseline PISA scores and the presence of periodontal pockets ≥6mm at dental screening were different between patients with and without bone healing problems, although the difference was not significant. There seems to be a trend, however, and our study may have been underpowered to find a significant difference.

Oral foci of infection

Compared to our retrospective study [2] that included 80 patients between January 2004 and December 2008 with a mean follow-up of 26 months subjected to conventional radiotherapy, a comparable percentage of patients presented with oral foci of infection (75% vs. 79%). Again, oral foci consisted mainly of periodontal disease, which is comparable to the percentage of patients with periodontal problems (68%) in the small study of Bueno *et al* [21]. Approximately 10% of Dutch adults have severe periodontal disease [22]. Apparently, poor periodontal health is common amongst HNC patients [2,23,24] and might be the cause of bone-related oral sequelae post-radiotherapy.

Bone healing problems and ORN

Bone healing problems were observed in 11 out of 56 patients (20%). We diagnosed 6 patients with delayed wound healing and 1 with lingual mandibular sequestration, which was not defined as ORN because healing occurred within 3 months after minimally invasive surgery (sequestrectomy). The immediate surgical intervention in case of exposed bone, as done in our hospital, may result in a more rapid healing compared to observation. This approach seems to give a lower incidence of low-grade ORN.

ORN was reported in 7% of our patients after IMRT compared to 11% in our retrospective 3-dimensional conformal radiation therapy (3D-CRT) study [2]. The prevalence of ORN as reported in the literature is highly variable [6] and the reported outcomes on occurrence of ORN after IMRT are limited. Our findings suggest a reduced rate of ORN following the clinical introduction of IMRT [25-27]. It has been suggested, however, that the latency time to develop jaw complications after IMRT is longer. Nevertheless, after 3 years the risk of developing jaw complications appears to be equal to that for non-IMRT treatment [28]. Nabil *et al* [6]

Table 3. Demographics, clinical characteristics and baseline dental data of the study group (n=56)

	Variable	Category	Number of patients dentate during follow-up Total n=51	Number of patients edentate during follow-up* Total n=5
Demographics	Age, years	Mean (SD)	59 (8.5)	62 (5.4)
	Gender	Male / Female	32 / 19	4 / 1
Clinical characteristics	Tumor site	Oral cavity	25	1
		Oropharynx	26	4
	T-classification	T1	10	1
		T2	17	2
		T3	6	0
		T4	17	2
		Not reported	1	0
	N-classification	N0	17	1
		N1	7	0
		N2	25	4
		N3	1	0
		Not reported	1	0
	Cumulative IMRT dose	Median [IQR]	70 [66-70]	70 [70-70]
	Frequency of IMRT	5 / week	42	3
		6 / week	9	2
	Primary IMRT		10	1
	Postoperative IMRT		14	0
	Primary CHIMRT		17	4
	Postoperative CHIMRT		10	0
	Chemotherapy type	Carboplatin / 5-FU	18	4
		Cisplatin	7	0
		Cetuximab	2	0
	Wound closure	Primary	9	0
		Skin graft / flap	15	0
	Self-reported smoking	Yes / In the past / No / NR	16 / 17 / 17 / 1	4 / 0 / 1 / 0
	Alcohol consumption	Yes / No	40 / 11	3 / 2
Baseline dental data	Number of teeth	Median [IQR]	24 [18-27]	11 [8.5-17]
	Plaque score	Median [IQR]	50 [25-75]	70 [45-80]
	Bleeding score	Median [IQR]	30 [20-60]	70 [33-95]
	PISA	Median [IQR]	349 [131-863]	533 [170-1509]
	DMFS	Median [IQR]	77 [60-102]	118 [88-120]

* After dental screening and pre-radiation treatment of oral foci, 5 patients needed a full mouth clearance.
SD= standard deviation; IQR= inter quartile range; IMRT= intensity modulated radiation therapy; CHIMRT= intensity modulated radiation therapy with chemotherapy; DMFS= decayed missing filled surfaces. The range of scores is 0-128. NR; Not reported

suggested a median/mean follow-up of >3 years, since 90% of ORN cases were reported within 3 years after radiotherapy. Our median follow-up was shorter than in the studies referred to, and more cases of ORN may develop in our cohort in the future. However, all cases of ORN in this study occurred in the first 7 months after IMRT had ended, so we do not expect many new cases to occur.

Studer *et al*. [25] reported 5 cases of ORN in 304 patients (1.6%) with oropharyngeal or oral cavity carcinoma treated with IMRT, with a follow-up between 5 and 86 months [25]. Gomez *et al*. [27] included 168 patients with a follow-up between 0.8 and 89.6 months; they reported a low incidence of ORN (1%). However, 54% of the included patients in the latter study had a tumor located outside the oral cavity or oropharynx, resulting in a lower radiation dose to the jaws, which might be accompanied by a lower incidence of ORN. Both studies [25,27] did not report how many patients received post-operative or primary IMRT, which may have influenced the outcomes on ORN since it is a known risk factor [7]. A complete lack of ORN was reported by Ben-David *et al.* [26]. They suggested that the reduction in the ORN rates could be attributed to more conformal dose distributions and to better prophylactic care and ongoing dental care.

Our oral care protocol did not change in the years between the retrospective and prospective study, although it was more strictly executed prospectively, with only 1 patient that was not treated according to protocol compared to 15 patients in the retrospective study [2]. Those 15 patients received pre-radiotherapy initial periodontal therapy for teeth with pockets ≥6mm, instead of tooth extraction, and they were particularly at risk of developing ORN. The improved implementation of the dental screening protocol may have decreased our ORN prevalence, as suggested by others [26], and this might explain the weaker relationship between periodontal disease and ORN found in the present study compared to the retrospective study [2]. Nevertheless, periodontal disease is still the only factor that we found to be associated with bone healing problems.

Periodontal treatment might have a short-term (6 months) positive effect on periodontal breakdown [21], but the present study, with a median of 24 months of follow-up, showed that progression of periodontal pocket depth was frequently observed after IMRT (24%). This percentage is even higher than the 18% reported in the retrospective study [2].

In our study on oral microflora [29], we found an almost immediate effect after the elimination of oral foci of infection, with a decrease of periodontal pathogens. However, rather high percentages of periodontal pathogens were still present in our HNC patients 1 year after IMRT and may have caused the observed progression of pocket depth.

Conclusion

This study showed that patients with periodontal disease before IMRT/CHIMRT are prone to develop bone healing problems during post-radiotherapy follow-up. The protocol was considered equally effective for those treated with IMRT/CHIMRT as compared to patients treated with conventional radiotherapy. Post-radiotherapy oral and dental morbidity seen in IMRT/CHIMRT patients is comparable to that seen in patients treated with conventional radiotherapy.

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Chapter 6

Effect of leaving chronic oral foci untreated on infectious complications during intensive chemotherapy

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Abstract

Background: Leukemic patients receiving intensive chemotherapy and patients undergoing autologous stem cell transplantation (ASCT) are routinely screened for oral foci of infection to reduce infectious complications that could occur during therapy. In this prospective study we assessed the effect of leaving chronic oral foci of infection untreated on the development of infectious complications in intensively treated hematological patients.

Methods: We included and prospectively evaluated all intensively treated leukemic patients and patients undergoing ASCT who were referred to our medical center between September 2012 and May 2014 and who matched the inclusion/exclusion criteria. Acute oral foci of infection were removed before chemotherapy or ASCT, while chronic oral foci were left untreated.

Results: In total 28 leukemic and 35 ASCT-patients were included. Acute oral foci of infection were found in 2 leukemic (7%) and 2 ASCT-patients (6%), chronic oral foci of infection in 24 leukemic (86%) and 22 ASCT-patients (63%). Positive blood cultures with microorganisms potentially originating from the oral cavity occurred in 7 patients during treatment, but were uneventful on development of infectious complications.

Conclusion: Our prospective study supports the hypothesis that chronic oral foci of infection can be left untreated as this does not increase infectious complications during intensive chemotherapy.

Introduction

Patients diagnosed with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma (HL) are usually treated with high-dose chemotherapy upfront or in a salvage setting. High-dose chemotherapy causes severe neutropenia (absolute neutrophil count <500/μL) for a certain period of time, which puts patients at high risk of infections, sepsis and septic shock [1]. Patients undergoing high-dose chemotherapy are also prone to develop oral side effects, such as oral mucositis, oral dryness, taste changes, and local and systemic infections [2]. Both neutropenia and oral mucositis significantly increase the risk for infectious complications during chemotherapy in these patients.

Hematologic patients subjected to high-dose chemotherapy are routinely screened for oral foci of infection before starting intensive treatment, since oral foci of infection may cause complications during treatment. Acute exacerbation of oral foci of infection is presumed to result in bacterial translocation from the oral cavity to the blood. To minimize the risks of developing oral problems and to reduce the chance of developing neutropenic fever, oral foci of infection which are anticipated to cause problems during chemotherapy are routinely eliminated. In our hospital, a team of oral maxillofacial surgeons, hospital dentists, and dental hygienists screen the patients for oral foci of infection before onset of cancer therapy.

It is still unclear which specific oral disorders have to be considered as an oral focus of infection in high-dose chemotherapy patients, which is also the case in head and neck radiotherapy [3]. Furthermore, the oral side effects of chemotherapy are essentially temporary and reversible, so the risk of developing complications due to oral foci of infection is not higher than in healthy subjects once patients have recovered from chemotherapy [4]. This is in contrast to head and neck radiotherapy, where the risk of oral foci of infection causing severe morbidity (like osteoradionecrosis) remains high or even increases after completion of radiotherapy [5]. Thus, the efficacy of dental screening for oral foci of infection in high-dose chemotherapy patients is questionable.

Moreover, leukemic patients usually have to start chemotherapy shortly after diagnosis. Consequently, if oral foci of infection are found during pre-treatment dental screening, insufficient time is available for effective dental treatment before starting chemotherapy. The decreased healing capacity during the phase of untreated leukemia is also a factor.

Following intensive chemotherapy, leukemic patients are expected to experience severe neutropenia for at least 3 weeks with episodes of neutropenic fever and relatively mild oral mucositis, whereas patients subjected to ASCT are expected to experience severe neutropenia for 1-2 weeks, but with a considerably higher chance of severe oral mucositis [6]. Both leukemic patients and patients treated

with high-dose chemotherapy followed by ASCT were included in this study, because the effects of an oral focus of infection and pre-chemotherapy dental treatment might be different due to the difference in duration of neutropenia and severity of oral mucositis between these groups.

Previous studies had mixed patient groups and/or a small number of patients [7,8] or reported on the need for treatment of postendodontic asyptomatic periapical radiolucencies [9].

This prospective study tested the hypothesis that chronic oral foci of infection do not have to be eliminated before intensive chemotherapy in leukemic patients subjected to intensive chemotherapy and MM/NHL/HL patients subjected to high-dose chemotherapy and ASCT. An oral focus of infection was considered chronic if that focus had not exacerbated and was asymptomatic during the previous 3 months.

Materials and methods

Patients

All patients diagnosed with AML or ALL before remission-induction chemotherapy and patients diagnosed with NHL/HL or MM before high-dose chemotherapy and ASCT, who were referred to the University Medical Center Groningen between September 2012 and May 2014, and who met the inclusion criteria, were included in this study. The medical ethical committee of the University Medical Center of Groningen approved our study protocol (METC 2012/170). AML-patients were treated with Cytarabine (Ara-C) based chemotherapy combined with anthracycline. ALL-patients were treated with intensive chemotherapy according to HOVON-100 and HOVON-71 study protocols [10]. NHL/HL-patients were treated with BEAM and ASCT [11,12] and MM-patients with high-dose melphalan (100mg/m^2 on days -3 and -2) before ASCT [13]. BEAM is a combination of carmustine (BiCNU®), Etoposide, Cytarabine and Melphalan.

Patients were included in this study if a pre-chemotherapy/pre-ASCT dental screening was done in the UMCG, if they were fully or partially dentate and were >18 years. Patients were excluded if they were not treated according to the study protocol on the treatment of acute and chronic oral foci.

Dental screening

Standard dental screening consisted of:

- intra-oral screening for mucosal and dental pathologies;
- panoramic radiograph and periapical dental radiographs when indicated, e.g., when apical problems were suspected on the panoramic radiograph or other abnormalities were seen;
- periodontal examination including probing pocket depth measurements, gingival recession, mobility and furcation measurements. Plaque and bleeding scores were assessed as a percentage of the total number of sites with plaque respectively bleeding on probing. To quantify periodontal disease, the periodontal inflamed surface area (PISA) was used [14];
- inquiry about oral health maintenance and the number of annual dental visits.

Additionally, a baseline throat swab and subgingival samples were taken during the dental screening.

Elimination of oral foci of infection

Acute oral pathology and/or teeth causing pain or other symptoms were eliminated pre-chemotherapy, while chronic oral foci were not eliminated preceding the chemotherapy based on the study by Toljanic et al. (1999).

Data sampling before and during chemotherapy

On the first day of hospitalization and before the start of chemotherapy, throat and rectal swabs were collected. Subsequent throat and rectal swabs were taken weekly during hospitalization (standard care). Hematology nurses daily checked the oral cavity for oral mucositis, according to the WHO mucositis grading scale [15].

Standard care during chemotherapy

All included patients hospitalized for high-dose chemotherapy were given selective digestive decontamination (SDD) therapy consisting of oral amphotericin B or fluconazole, colistine, and/or trimethoprim/sulfamethoxazole or ciprofloxacin [16,17]. During fever (body temperature ≥38.5°C), irrespective of the neutropenic status of the patient, blood cultures and central line cultures were taken, and after which a piperacilline/tazobactam therapy was started. Radiography of the lungs was performed to exclude pneumonia. Urine cultures were taken. *Clostridium difficile* colitis was excluded. The patients were physically examined by the hematologist or internal medicine physician on a daily basis and additional blood cultures were taken after 48-72 hours of fever.

Oral care and oral problems during chemotherapy

All patients were advised to continue normal daily oral care (tooth brushing and/or interdental cleaning) as long as possible. Additionally, or when brushing was too painful, patients were advised to rinse the oral cavity with saline solution 4 times per day and not to wear their removable prosthesis, if any, during chemotherapy courses.

ASCT-patients were seen by the dental hygienist for oral examination 3 times per week during their hospital admission. Leukemic patients were seen by the dental hygienist when oral complaints had developed.

If untreated chronic oral foci of infection became acute during chemotherapy or between chemotherapy courses, piperacilline/tazobactam was given and appropriate dental treatment was rendered.

Follow-up after treatment
Patients were followed during the course of their hematologic treatment up until 6 weeks after treatment had ended. Patient' charts were reviewed for oral problems during and after treatment. After treatment had ended, patients were seen weekly by the hematologist for check-ups at the outpatient hematology department.

Microbiological sampling and analysis
To determine the possible oral origin of microorganisms found in blood cultures, bacteriological samples were taken and compared to the results of blood cultures.

A throat swab of the tonsil area was taken according to the method described by Syed and Loesche (1972). Microbiological analysis of throat swabs was performed according to standard procedures and included detection of yeasts, *Staphylococcus aureus* and aerobic Gram-negative rods. Aerobic incubation took place for 48 hours at 35°C.

Periodontal (subgingival) samples were taken from the deepest, bleeding or suppurating pocket in each quadrant of the dentition. Two sterile paper points were inserted to the depth of the pockets, left in place for 10 seconds and were collected and pooled in 2ml of reduced transport fluid [18]. Periodontal samples were processed using culturing technique as described by Van Winkelhoff et al. (1985) and Van Steenbergen et al. (1993). Anaerobic cultivation was performed to determine the total periodontal bacterial load and presence and levels of *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia, Fusobacterium nucleatum, Parvimonas micra,* and *Campylobacter rectus.* If Gram-negative aerobic rods or staphylococci were found in positive blood cultures, periodontal samples were also analyzed for the presence and levels of these microorganisms.

Statistical analysis
All data were recorded using a standardized study form designed for this study. A gap in a sequence of mucositis score values was filled with the same value given before and after a gap. In case of different values before and after a gap, the lowest value was imputed. Data were analyzed using descriptive statistics in SPSS Statistics 22 (IBM Corp., Armonk, NY, USA). Testing for significance was done using Chi-Square for binary outcomes (prevalence, presence) and Mann-Whitney tests for continuous outcomes. Values of $p<0.05$ were considered significant.

Results

Demographics
In total, 64 patients were included. Statistical analysis was done with 63 patients, since 1 patient with an acute oral focus was not treated according to the inclusion criteria. Demographics of patients before onset of hematological treatment are shown in Table 1. In the leukemic group, 28 patients were included, of which 23 were diagnosed with AML, 4 with ALL and 1 with CML blast crisis. In the ASCT-group, 35 patients were included, of which 21 were diagnosed with MM, 13 with NHL, and 1 with HL. There was no statistically significant difference between the groups regarding male/female ratio and age (Table 1).

During the 6 weeks of follow-up after hematologic treatment, 5 of 28 leukemic patients died. This was due to refractory disease in one patient, recurrence of disease in 2 patients, and toxicity of chemotherapy with subsequent complications in 2 patients, with no contribution of oral foci. None of the ASCT-patients died before end of follow-up.

Oral foci of infection
Outcomes of dental screening are presented in Table 1. In the leukemic group, 24 out of 28 patients (86%) presented with chronic oral foci of infection. Amongst them were 2 patients who had both acute and chronic foci. In the ASCT-group, 22 out of 35 patients (63%) presented with chronic oral foci of infection. One patient had both acute and chronic oral foci. The specific acute and chronic oral foci types are presented in Table 1. Data on visits to the dentist and dental hygienist and data on oral hygiene are also presented in Table 1. The baseline median PISA and bleeding scores were significantly higher in the leukemic group compared to the ASCT-group ($p=0.024$ and $p=0.005$, respectively).

Periodontal samples
The majority of patients in this study had periodontal infection associated with opportunistic oral pathogens. *Fusobacterium nucleatum, Parvimonas micra, Prevotella intermedia*, *Tannerella forsythia* and *Campylobacter rectus* were isolated in 79%, 71%, 32%, 31% and 24% of patients, respectively. Occasionally, *Aggregatibacter actinomycetemcomitans* (2%) and *Porphyromonas gingivalis* (5%) were isolated. No significant differences were found between the leukemic and the ASCT-group regarding the prevalence of periodontal pathogens. In our study cohort, no periodontal pathogens were cultured from any of the blood cultures (Table 2).

Blood cultures of the leukemic group
Blood cultures were indicated because of neutropenic fever in all 28 leukemic patients (100%). Twenty-five patients (89%) had a total of 57 positive blood cultures. The microorganisms found in the blood cultures are presented in Table 2.

Blood cultures of the ASCT-group
Blood cultures were indicated because of neutropenic fever in 22 out of 35 ASCT-patients (63%), which is significantly lower than in the leukemic group ($p=0.0001$). Out of these 22 patients, 11 (50%) had 1 or more positive blood cultures (Table 2), which was significantly lower than in the leukemic group (89%) ($p=0.002$).

Table 1. Demographic characteristics of the included patients before hematological treatment.

	Leukemic group	ASCT-group
Male/Female	16/12	20/15
Age Mean (SD)	51 (12.4)	51 (10.1)
	Number of patients (% of group)	
Last visit to dentist		
Last 6 months	19 (68%)	19 (54%)
Last year	3 (11%)	7 (20%)
>1 year ago	3 (11%)	6 (17%)
Not reported	3 (11%)	3 (9%)
Visit to dental hygienist		
At least twice a year	6 (21%)	8 (23%)
Once a year	3 (11%)	5 (14%)
Never	18 (64%)	21 (60%)
Not reported	1 (4%)	1 (3%)
Oral complaints*		
No complaints	21 (75%)	28 (80%)
Not reported	1 (4%)	0 (0%)
Currently	7 (25%)	7 (20%)
Last 3 months	10 (36%)	9 (26%)
Dental status		
Number of teeth	25 (mean); range 10-32	25 (mean); range 9-30
Oral foci of infection total**		
No oral foci of infection	4 (14%)	12 (34%)
Acute oral foci of infection	2 (7%)	2 (6%)
Chronic oral foci of infection	24 (86%)	22 (63%)
Acute oral foci of infection		
Active pus-producing fistula	1 (4%)	1 (3%)
Symptomatic periapical granuloma	1 (4%)	1 (3%)
Chronic oral foci of infection		
Periodontal pockets ≥6mm	13 (46%)	11 (31%)
Periapical granuloma	10 (36%)	10 (29%)
Initial endodontic treatment	2 (7%)	0 (0%)
Furcation involvement	2 (7%)	2 (6%)
Retained roots	2 (7%)	1 (3%)
Fully or partially impacted teeth	3 (11%)	3 (9%)
Caries profunda	2 (7%)	1 (3%)
Follicular cyst	0 (0%)	2 (6%)
Periodontal condition		
Healthy periodontium	0 (0%)	3 (9%)
Periodontal pockets ≥4mm	27 (96%)	32 (91%)
Periodontal pockets ≥5mm	19 (68%)	21 (60%)
Periodontal pockets ≥6mm	13 (46%)	11 (31%)
Periodontal status not reported	1 (4%)	0 (0%)
PISA score in mm^2 (median, IQR)[a]	533 [199-834]	228 [135-478]
Plaque score (median, IQR)[b,c]	30% [19-50]	25% [20-50]
Bleeding score (median, IQR)[b,d]	45% [20-80]	20% [10-40]

ASCT= autologous stem cell transplantation
SD= Standard Deviation
IQR= interquartile range
*; Total sums up to >28 and >35 patients, because some patients had both oral complaints currently and during the last 3 months.
**; Total sums up to >28 and >35 patients, because some patients had both acute and chronic oral foci of infection
***; Total sums up to >24 and >22 patients, because some patients had more than 1 type of chronic oral foci of infection
[a] ; The difference between the groups is significant (*p*=0.024) using a Mann-Whitney test
[b] ; Plaque- and bleeding scores were given as an estimated percentage of the total number of measured sites, after probing periodontal pockets
[c] ; The difference between the groups is not significant (*p*=0.56) using a Mann-Whitney test
[d] ; The difference between the groups is significant (*p*=0.005) using a Mann-Whitney test

Due to rounding of the percentages, total sums are not always exactly 100%.

Table 2. Microorganisms in positive blood cultures and their primary ecological niches, ordered by frequency of occurrence.

Microorganisms cultured from blood	Primary ecological niches*	Number of culture-positive subjects	
		Leukemic patients n=25	ASCT**-patients n=11
Staphylococcus epidermidis	S, M	17 (61%)	7 (20%)
Staphylococcus haemolyticus	S	8 (29%)	1 (3%)
Enterococcus faecium	I, S, **O**, E	7 (25%)	1 (3%)
Streptococcus mitis	M, **O**, I, V, S	4 (14%)	1 (3%)
Micrococcus luteus	S, E, **O**, **OP**	3 (11%)	0
Staphylococcus hominis	S	3 (11%)	0
Bacillus mycoides	E	0	1 (3%)
Burkholderia genus REC A	E, **O**	1 (4%)	0
Lactobacillus rhamnosus	**O**	1 (4%)	0
Pantoea gavinae	E	1 (4%)	0
Rothia mucilaginosa	**OP**	1 (4%)	0
Serratia marcescens	S, I	1 (4%)	0
Staphylococcus aureus	S, N, **T**, P, **O**	0	1 (3%)
Staphylococcus capitis	S, **O**	1 (4%)	0
Streptococcus parasanguinis	M, I, V, S, **O**	1 (4%)	0

* The bold letters in this table indicate the microorganisms related to the oral cavity, oropharynx or throat.
**ASCT= autologous stem cell transplantation
I, intestines; S, skin; O, oral cavity; E, environment (plants, animals, soil); OP, oropharynx, M, mucosal tissues, V, vagina; N, nose; T, throat; P, perineum
More than one microorganism was cultured in some patients and some patients had more than 1 positive blood culture, so the total sums up to >25 leukemic and >11 ASCT-patients.

Chronic oral foci of infection related to various clinical parameters

No significant differences were found between patients with chronic oral foci of infection (n=46) compared to patients without chronic oral foci of infection (n=17) regarding positive blood cultures (p=0.798), duration of neutropenia (p=0.066) or fever (p=0.059), duration of mild (p=0.107) or severe oral mucositis (p=0.398), and prevalence of mild (p=0.273) or severe oral mucositis (p=0.510). Moreover, no significant differences were found when performing a subgroup analysis (leukemic and ASCT). No differences were found regarding duration of neutropenia and fever, between patients without chronic oral foci of infection at dental screening, patients with untreated chronic oral foci of infection, and patients with treated acute oral foci of infection.

Table 3. Comparison between patients with positive blood cultures with microorganisms possibly related to the oral cavity and patients with positive blood cultures with microorganisms unrelated to the oral cavity.

Variables	Patients with microorganisms related to the oral cavity (Total n=7)	Patients with microorganisms unrelated to the oral cavity (Total n=29)	p- value
Baseline presence of acute oral foci of infection	0	3	p=0.374*
Baseline presence of chronic oral foci of infection	6	21	p=0.466*
Baseline presence of periodontal pockets ≥ 6mm	2	12	p=0.533*
Baseline presence of periapical granuloma	5	11	p=0.109*
Baseline presence of caries profunda	1	2	p=0.526*
Baseline presence of impacted teeth	2	4	p=0.346*
Smoking yes/no	1/6	7**/21	p=0.546*
	Median [IQR]	Median [IQR]	
Duration of neutropenia in days	11 [7-41]	23 [8-46]	p=0.531
Duration of fever in days	9 [4-24]	9 [4.5-15]	p=0.969
Duration of severe oral mucositis in days in 17 patients with severe oral mucositis	3.5 [1.25-8] n=4	5 [2.5-9.5] n=13	p=0.477
PISA-score in mm^2	419.5 [94.5-1025]***	412 [142-650.75]**	p=1.0
Plaque scores in %	25 [10-57.5]***	30 [20-50]**	p=0.494
Bleeding scores in %	30 [7.5-76.25]***	30 [20-50]**	p=0.612
Age in years	49 [28-62]	50 [44-60]	p=0.969

IQR= interquartile range
PISA= periodontal inflamed surface area
*Results Chi-Square tests. All other variables were tested using Mann-Whitney tests.
**Because of missing value, n=28
*** Because of missing value, n=6

Microorganisms found in blood culture possibly related to oral cavity

In our study cohort, no periodontal pathogens were initially cultured from any of the positive blood cultures (Table 2). After specific culturing for Gram-negative aerobic rods and staphylococci, which was done if these microorganisms were found in positive blood cultures, 1 match was found between positive blood cultures and periodontal samples for *Staphylococcus haemolyticus*. Microorganisms potentially originating from the oral cavity, oropharynx and/or throat were found in the blood cultures of 7 patients; 5 leukemic and 2 ASCT-patients (indicated by bold letters in Table 2). These microorganisms were not periodontal pathogens and were not found in any of the throat swabs.

Table 3 shows that no possible contributing factors were found that differed significantly for the 7 patients with positive blood cultures with microorganisms possibly related to the oral cavity, compared to the patients with positive blood cultures with microorganisms unrelated to the oral cavity (n=29). Furthermore, 4 of these 7 patients had oral complications during chemotherapy unrelated to oral foci of infection (oral mucositis n=4, herpes simplex virus n=1 and pulpitis n=1).

Neutropenia, fever and oral mucositis

A significantly higher prevalence of severe oral mucositis (p=0.014) was found amongst leukemic patients (57%) compared to ASCT-patients (26%). No oral mucositis was observed in 47% of the ASCT-patients, which was significantly higher than in leukemic patients (11%; p=0.002). No significant differences were found between leukemic patients and ASCT-patients regarding the duration (p=0.890) of severe oral mucositis. A median of 5 days was seen in both groups. There was no relation between the severity of mucositis and chronic oral foci of infection at baseline (p=0.269).

No significant differences were found between patients with positive blood cultures compared to patients with negative blood cultures regarding the duration (p=0.648) or prevalence of severe oral mucositis (p=0.717). However, patients with positive blood cultures had a significantly longer duration of mild oral mucositis than patients with negative blood cultures (p=0.039). Prevalence of mild oral mucositis was not significantly different between patients with positive or negative blood cultures (p=0.700).

Periodontal health and positive blood cultures

No significant differences were found between patients with positive blood cultures compared to patients with negative blood cultures regarding periodontal inflamed surface area as measured with PISA at baseline (p=0.379). In line with this observation, patients with positive blood cultures did not have significantly higher plaque and bleeding scores at baseline compared to patients with negative blood cultures (p= 0.338 and p=0.990, respectively).

Oral complications during hematologic treatment

During hematologic treatment, oral complications other than oral mucositis were seen (n=15; 24%; 9 leukemic and 6 ASCT-patients). The prevalence of exacerbation of chronic oral foci during hematologic treatment was 4% in this study. One AML-patient with an acute exacerbation of an asymptomatic periapical granuloma present at baseline and 1 ASCT-patient with an acute exacerbation of pre-existent gingivitis, which were both uneventful. Oral complications not related to chronic oral foci of infection observed were oral pain (n=3), oral herpes simplex infection (n=5), peri-oral herpes simplex (n=3), mandibular swelling (n=1) and oral candidiasis (n=1). No significant differences were found between patients with oral complications (n=15) and patients without oral complications (n=48) regarding presence of acute (p=0.954) or chronic oral foci of infection (p=0.197), periodontal disease (pockets ≥6 mm) (p=0.437), PISA-score (p=0.474), smoking (p=0.102), plaque scores (p=0.941), bleeding scores (p=0.456), age (p=0.127), positive blood cultures (p=0.453), or a significantly different duration of neutropenia (p=0.398), fever (p=0.278) or severe oral mucositis (p=0.214).

Discussion

The results of this prospective study show that leaving chronic oral foci of infection untreated before intensive chemotherapy and ASCT (and during neutropenia with or without oral mucositis) does not increase the morbidity of the cancer treatment, in particular regarding infectious complications such as bacterial sepsis, nor does it increase mortality.

A significantly longer median duration of neutropenia, significantly more positive blood cultures and significantly more severe oral mucositis were found in leukemic patients compared to ASCT-patients. This might explain why more leukemic patients (18%) had positive blood cultures with microorganisms possibly related to the oral cavity than ASCT-patients (6%). However, positive blood cultures were not associated with a specific microorganism present in the oral cavity and the gastrointestinal tract as assessed with cultures from periodontal samples, throat and rectal swabs.

Comparison with previous studies

Neutropenic fever was seen in all leukemic patients, which corresponds with literature reporting neutropenic fever seen in 85-97% of neutropenic episodes [19,20]. In our study, neutropenic fever was seen less frequently in ASCT-patients (63%), which was expected based on previous studies (39%-84%) [21-23]. Positive blood cultures were found in 89% of leukemic and 50% of ASCT-patients in our study, which is high compared to data from the literature [19,20,24,25]. However, comparing our data with that from previous studies is difficult due to varying patient groups and inconsistencies in reporting.

Instead of systemic complications of chronic oral foci, local complications, such as interchemotherapy acute conversions of previously diagnosed chronic dental disease, were assessed by Toljanic et al (1999). An incidence rate of 4% was reported, which is comparable to our data. However, both hematologic and solid malignant neoplasms were included in Toljanic's study, which hampers comparison, and, more importantly, no information was provided on blood cultures.

Bacteremia was predominately caused by Gram-positive bacteria in our study. In line with our results, previous studies described a shift in time from the predominance of Gram-negative bacteria to the predominance of Gram-positive bacteria [26]. Staphylococcus epidermidis was most often found in our positive blood

cultures (Table 2). This microorganism is a common cause of bacteremia and is associated with central venous catheters, which were used in all of our patients [27]. In accordance with the studies by Sonis et al. (2001) and McCann et al. (2009), we found that patients with oral mucositis had a significantly longer duration of neutropenia and fever than patients without oral mucositis. The first prospective study with oral mucositis as the main objective showed severe oral mucositis in 46% of MM patients and 42% of NHL patients [6]. The lower percentage of severe oral mucositis among ASCT-patients in our study (26%) might be due to the fact that MM-patients receiving high-dose melphalan (n=21) were given ice-cubes in the mouth (cryotherapy) during chemotherapy infusion, as advised by the guidelines of MASCC/ISOO [28] and in other reviews [29,30].

Microorganisms potentially originating from the oral cavity, oropharynx and throat were found in the blood cultures of just 7 patients (Table 2). We expected the number of oral microorganisms found in blood cultures to be higher, since even tooth brushing, a seemingly harmless daily activity, can cause bacteremia with oral microorganisms [31]. Especially in immuno-compromised patients, as in our study, bacteremia is expected to occur more often and to last longer, increasing the chances of detecting the causative microorganism by blood culturing. The patients in our study with oral mucositis hardly brushed, but frequently rinsed the oral cavity, which could explain the lower frequency of bacteremia, together with the use of SDD.

Implications

The outcomes of our study indicate that chronic oral foci of infection without acute signs or symptoms can be left untreated in patients receiving high-dose chemotherapy and ASCT and/or intensive chemotherapy. This allows for a less aggressive approach with no removal of chronic oral foci of infection before starting chemotherapy. Such an approach is likely to be beneficial for hematologic patients, as removal of teeth may compromise nutrition, and malnutrition is associated with lower quality of life [32]. Tooth extraction also leads to a risk for infection, bleeding or delayed wound healing, which may require postponing oncologic treatment [33], or otherwise increase bacteremia with a higher chance of septic complications. For survivors, treatment of diseased teeth can be postponed until oncologic treatment is completed. Moreover, pre-chemotherapy dental work-up will be less time consuming when only acute oral foci of infection, seen in less than 10% of our patients, have to be treated instead of all the chronic oral foci seen in over 70% of our patients.

Suggestions for additional research

Future prospective studies with larger patient groups are needed, to see if leaving chronic oral foci untreated may lead to a significantly longer duration of fever and neutropenia, as our results showed a strong trend when comparing duration of neutropenia (p=0.066) and fever (p=0.059) in patients with and without chronic oral foci of infection. Future study methods should enable comparison between studies, as sample size calculation showed that over 4000 patients will be needed to find a significant difference between patients with and without chronic oral foci of infection, regarding positive blood cultures (respectively, 73% and 69% of those patients had positive blood cultures in our study). The cost-effectiveness of this less aggressive approach should be studied, and the improvement in quality of life may be confirmed in future studies.

In conclusion, our prospective study supports the hypothesis that chronic oral foci, if they had not exacerbated during the previous 3 months, do not have to be eliminated before intensive chemotherapy, as they do not increase infectious complications in these patients.

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Chapter 7

General discussion

General discussion

This thesis assessed the efficacy of pre-treatment dental screening in head and neck cancer (HNC) patients subjected to radiotherapy and in hematology patients subjected to intensive chemotherapy regarding complications during treatment and follow-up.

At the start of this PhD project, there was a lack of evidence for dental screening and elimination of oral foci of infection, especially considering new treatment modalities, such as intensity modulated radiation therapy (IMRT) with or without adjuvant chemotherapy. Based on the studies performed in this PhD study, it can be concluded that the assessed dental screening protocol was equally effective in patients treated with IMRT, IMRT combined with chemotherapy (CHIMRT) and in patients treated with conventional radiotherapy, since post-radiotherapy oral and dental morbidity seen was comparable. However, not all oral sequelae can be prevented and the need for further research remains.

It was found that in particular HNC patients with periodontal disease before radiotherapy were prone to develop bone healing problems after radiotherapy. Furthermore, in hematology patients, it was shown that chronic oral foci of infection can be left untreated as leaving these foci untreated does not increase infectious complications during intensive chemotherapy.

What to consider as an oral focus of infection?

Little evidence exists on the efficacy of elimination of oral foci of infection to prevent post-radiotherapy oral sequelae [1,2], nor is it clear what to consider as an oral focus of infection in specific patient groups. In our systematic review (**Chapter 2**), we found only low-level evidence to answer the questions of whether pre-radiation elimination of oral foci of infection in HNC patients is efficient and whether pre-radiation elimination of these oral foci should be mandatory. This review confirmed that most studies yet published did not even use a univocal definition of an oral focus of infection, or it was unclear what was considered an oral focus [3]. After using the same efficient dental screening protocol in both a retrospective (**Chapter 3**) and a prospective study (**Chapter 5**), we suggest that the following should be considered as an oral focus of infection in HNC patients:

- deep caries in which excavation may lead to pulpal exposure;
- active periodontal disease with pockets ≥6mm, furcation ≥grade 1, mobility >grade 1, gingival recession ≥ 6mm and especially a combination of these periodontal problems;
- non-restorable teeth with large restorations, especially those extending the gum line or with root caries, or those with severe erosion or abrasion;
- periapical granuloma and avital teeth;
- (partially) impacted or partially erupted teeth not fully covered by bone or showing radiolucency;
- cysts and other radiographic abnormalities.

As mentioned before, we showed that chronic oral foci of infection can be left untreated in hematology patients subjected to intensive chemotherapy, as this does not increase infectious complications during intensive chemotherapy (**Chapter 6**). The study described in chapter 6 also showed that what to consider as an oral focus of infection is dissimilar in chemotherapy patients than in patients submitted to radiotherapy. This is due to the fact that the adverse effects of chemotherapy are mainly reversible and that the risk of developing complications related to oral foci of infection is probably not higher than in healthy subjects, once the patient had recovered from oncologic treatment and blood levels have normalized. This is in contrast to radiotherapy, where the effects are mainly irreversible and the risk to develop complications remains a lifelong. Unlike previous studies that focused on acute conversions of previously diagnosed chronic dental disease [4], we focused on systemic complications of chronic oral foci of infection. Based on the outcomes of this prospective study, we recommend pre-chemotherapy dental screening and treatment of acute oral foci of infection in intensively treated leukemic patients and patients subjected to high-dose chemotherapy and autologous stem cell transplantation (ASCT) as follows:

ask and examine patients if they had any symptoms like tooth related or oral mucosa related pain, percussion or palpation tenderness of oral structures, fever related to oral pathology, swelling of oral tissues and/or tooth related purulent drainage that might be caused by a pathology related to the oral mucosal and/or dental hard tissues during the past 3 months. These acute oral problems and pathologies should be eliminated before the onset of chemotherapy.

Osteoradionecrosis

The results of our retrospective study (**Chapter 3**) suggest that patients presenting with severe periodontal disease at dental screening are prone to develop osteoradionecrosis (ORN), particularly when the periodontally affected teeth in these patients are not (aggressively) treated. Our prospective study (**Chapter 5**) showed that patients with periodontal disease before IMRT/CHIMRT were indeed prone to develop bone healing problems after IMRT/CHIMRT. The better execution of the dental screening protocol (teeth with pockets ≥6mm were extracted instead of maintained and treated with initial periodontal therapy) may have lowered our ORN prevalence and this might explain the less strong relation between periodontal disease and ORN found in the prospective study than in the retrospective study [5]. It has to be mentioned, however, that our study may have been underpowered to find a significant difference, but the results of our prospective study at least point towards the hazard of periodontal disease with regard to a higher risk of developing bone healing problems post-radiotherapy.

This hazard might increase during long-term follow-up, because due to the less reduced salivary flow rate seen after IMRT compared to conventional radiotherapy, the risk of developing rapidly progressing dental caries may reduce. As a results, teeth will be longer preserved in IMRT patients, increasing the risk to develop peri-

odontal problems which now have more time to develop.

To quantify periodontal disease, the periodontal inflamed surface area (PISA) was used in the prospective studies (**Chapter 5 and 6**) described in this thesis [6]. As PISA is a measure for inflammation load, it was very suitable to use in our hematology study (**Chapter 6**) assessing the effect of leaving chronic oral foci, such as periodontally affected teeth, on infectious systemic complications. However, when assessing the relation between periodontal disease and bone healing problems/ ORN, which is a local problem, we preferred to look at pocket progression at the tooth level (**Chapter 5**) as removal of teeth already greatly reduced the PISA score. Thus, PISA scores are not preferred in radiotherapy studies.

In our study on oral microflora (**Chapter 4**), we found an almost immediate effect after the elimination of oral foci of infection, with a decrease of periodontal pathogens. However, rather high percentages of periodontal pathogens were present after 1 year of follow-up and may have caused the progression of pocket depth observed. It is also suggested in literature that changes in cellularity, vascularity and reduced healing/remodeling potential of the periodontium contribute to the increased risk of periodontal involvement after radiotherapy [7]. Also, compromised oral hygiene and reduced salivary flow may underlie the progression of periodontal disease.

Guidelines pre-radiotherapy dental screening in head and neck cancer

Although no strict guidelines for pre-radiotherapy dental screening and elimination of oral foci exist, the studies in HNC patients in this thesis have shown that a strict execution of a dental screening protocol is mandatory. Not aggressively treating periodontally affected teeth pre-radiotherapy resulted in an increased risk for ORN (**Chapter 2**) and patients with periodontal disease before IMRT were prone to develop bone healing problems after IMRT (**Chapter 5**). Progression of periodontal pocket depth was observed in 24% of HNC patients after IMRT/ CHIMRT. The patients' periodontal status at dental screening and the probability of progression of periodontal disease after IMRT/CHIMRT should be considered carefully in dental treatment planning before radiotherapy. A strict execution of a well-defined dental screening protocol is likely to result in fewer post-radiotherapy extractions and therefore, less ORN since post-radiotherapy extractions are a well-known risk factor [8,9]. Although there is no literature available evaluating the economic impact of ORN [10], high costs are inevitable when for example surgical intervention and hyperbaric oxygen therapy are mandatory. Reducing the incidence of ORN is likely to reduce health care costs and more importantly, may prevent suffering from the patients.

It is recommended to perform a pre-radiotherapy dental screening for HNC patients subjected to radiotherapy according to an (as far as yet available) evidence-based protocol, as applied in our prospective study (Chapter 5). This screening should preferably be done at least 10-14 days before the start of radiotherapy to allow for healing of, e.g., extraction sites. Additionally, oral hygiene instructions

should be given. All patients need to be evaluated for periodontal disease, as periodontal disease, according to the results presented in Chapters 3 and 5, probably is a condition making subjects prone to develop ORN. Thus, the starting point of a pre-radiotherapy dental screening should be which teeth can be maintained, when considering (1) the long term prognosis of the teeth in relation to the disease status of the patient, (2) the patient's ability to maintain a proper level of oral hygiene depending on, amongst others, motivation and physical abilities and (3) the patient's susceptibility to develop ORN. A careful, frequent (at least twice a year), standardized oral follow-up with repeated oral hygiene instructions is needed after radiotherapy, at least in dentate patients.

Guidelines dental screening in intensively treated hematologic patients

Although no strict guidelines for pre-chemotherapy dental screening and elimination of oral foci exist, the hematology study in this thesis has shown that a less aggressive approach can be executed in leukemic patients subjected to intensive chemotherapy and in multiple myeloma (MM), non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma (HL) patients subjected to high-dose chemotherapy and ASCT (**Chapter 6**). Such an approach is likely to be beneficial for these hematologic patients, as removal of teeth just before or during neutropenic phases of their disease may compromise nutrition, and malnutrition is associated with a lower quality of life [11]. Tooth extraction directly before the start of intensive chemotherapy also leads to a risk for infection, bleeding or delayed wound healing, which may require postponing oncologic treatment [12], or otherwise increase bacteremia with a higher chance of septic complications. For survivors, treatment of diseased teeth can be postponed until oncologic treatment is completed and blood levels have normalized. Moreover, pre-chemotherapy dental work-up will be less time consuming and therefore less expensive, when only acute oral foci of infection, seen in less than 10% of our patients, have to be treated instead of all the chronic oral foci seen in over 70% of our patients scheduled for intensive chemotherapy.

Based on our study outcomes it is recommended to perform pre-chemotherapy dental screening in leukemic patients subjected to intensive chemotherapy and in MM/NHL/HL patients subjected to high-dose chemotherapy and ASCT. With regard to the dental screening, oral foci of infection should be defined as acute or chronic. Chronic oral foci of infection can be left untreated, while acute oral foci of infection should be eliminated, preferably before onset of chemotherapy or otherwise early thereafter.

Recommendations for future research

More prospective studies are needed with well-defined criteria for oral foci of infection, a clear description of which foci were eliminated and how, a detailed description of how dental screening was done, clearly described patient and tumor characteristics, and a detailed dental history and dental status. Although our pro-

spective study was a good start, a larger patient group would be preferable, especially regarding low incidence of oral sequelae such as ORN. In future studies, the oral problems that occur post-IMRT should be systematically recorded. Doing so would allow for a sound comparison of prospective studies which would result in a higher level of evidence for performing dental screening and eliminating oral foci of infection pre-radiotherapy than the mainly retrospective cohort studies that are currently available. Amongst others, the relation between periodontal disease and bone healing problems can be assessed in a meta-analysis once sufficient comparable prospective studies are available.

We will continue to follow our HNC cohort, which will provide the readership with long term data on the efficacy of dental screening in preventing oral sequelae such as ORN in IMRT/CHIMRT patients.

Regarding intensive chemotherapy patients, prospective studies with larger patient groups are needed, to assess whether leaving chronic oral foci untreated may lead to a significantly longer duration of fever and neutropenia, as our results showed a strong trend when comparing duration of neutropenia (p=0.066) and fever (p=0.059) in patients with and without chronic oral foci of infection. If this trend would be found statistically significant, patient factors such as the level of oral hygiene and PISA scores may play an important role and have to be assessed, as bad oral hygiene and a large periodontal inflamed surface area may increase the risk for bacteremia with oral microorganisms. Frequent bacteremia may results in a longer duration of neutropenia and fever. The assessed protocol of leaving chronic oral foci of infection untreated could still be executed, however, since we did not see infectious complications related to oral microorganisms. The alternative, which is tooth extraction, leads to a risk for infection, bleeding or delayed wound healing, which may require postponing oncologic treatment [12], or otherwise increase bacteremia with a higher chance of septic complications.

To be able to find a significant difference between patients with and without chronic oral foci of infection, regarding the number of positive blood cultures (respectively, 73% and 69% of those patients had positive blood cultures in our study) a sample size calculation showed that over 4000 patients will be needed. As such high numbers are needed to find a significant difference, it is important that the applied methods in future studies allow comparison between studies, since it is not feasible for a single institution or even multicenter studies to include such a high number of patients.

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Chapter 8

Summary

Summary

Pre-treatment dental screening of, amongst others, head and neck cancer (HNC) patients and hematology patients aims to identify and eliminate oral foci of infection to prevent oral sequelae during or post-treatment. The efficacy of dental screening is yet not evidence based, it is even not set whether it is effective at all, particularly in chemotherapy patients. While radiotherapy to the head and neck region is accompanied by a life-long risk of developing severe oral sequelae related to irreversible radiation injury to hard and soft tissues, the changes induced in these tissues by chemotherapy are mostly reversible. Thus, what is considered an oral focus of infection needing treatment might differ between patients scheduled for radiotherapy or chemotherapy as, when the effects of oncologic treatment are reversible, the risk of developing complications related to oral foci of infection is probably not higher than in healthy subjects. Moreover, the recent introduction of intensity modulated radiation therapy (IMRT) has changed the dose distribution in soft and hard tissues within the radiation portal and thus might be accompanied by another risk profile on radiation sequelae than conventional radiotherapy.

The general aim of this thesis was to assess the efficacy of pre-treatment dental screening in HNC patients subjected to radiotherapy and in hematology patients subjected to intensive chemotherapy regarding complications during treatment and follow-up.

A systematic review was performed to analyze the available evidence on the efficacy of pre-radiation elimination of oral foci of infection in preventing oral sequelae (**Chapter 2**). A literature search was conducted (MEDLINE/EMBASE) for papers published up to May 2014. Papers on HNC patients subjected to pre-radiation dental screening, (chemo)radiation and oral follow-up were included. Of the 1770 identified papers, 20 studies fulfilled the inclusion criteria of which 17 were retrospective. A great heterogeneity in patient groups, dental screening techniques, definitions of oral foci of infection and techniques for eliminating foci was found. Most papers lacked essential details on how dental screening was performed and a clear definition of an oral focus of infection. The evidence for efficacy of elimination of oral foci of infection to prevent post-radiotherapy oral sequelae was inconclusive. Consequently, the efficacy of pre-radiation elimination of oral foci of infection remains unclear. No conclusions could be drawn about a definition of an oral focus of infection and whether pre-radiation elimination of these foci should be mandatory.

In **Chapter 3,** a retrospective study is described in which an inventory was made of oral foci detected during pre-radiation dental screening and follow-up of those patients in order to assess risk factors for developing oral sequelae after radiotherapy. Charts of 185 consecutive HNC patients, subjected to a pre-radiation dental screening between January 2004 and December 2008, were reviewed. Eighty (partially) dentate patients scheduled for curative head and neck radiotherapy met the inclusion criteria. Oral foci were found in 76% of patients, predominantly periodontal disease. Osteoradionecrosis (ORN) had developed in 9 out of 80 patients (11%). Overall, patients presenting with periodontal pockets ≥6 mm at dental screening had an increased risk of developing ORN compared to the total group of patients. Patients in whom periodontal disease treatment was composed of initial periodontal instead of removal of the affected teeth, the risk of developing ORN was even higher. A worse periodontal condition at dental screening and initial periodontal therapy to safeguard these patients to develop severe oral sequelae after radiotherapy were shown to be major risk factors of developing ORN.

It is not yet known how changed treatment modalities for HNC affect the composition of the oral flora. In **Chapter 4** a prospective study is described that assessed the effects of a variety of treatments for HNC on the oral microflora. This study was composed of 82 patients, diagnosed with a primary oral or oropharynx carcinoma, seen for a pre-treatment dental screening between May 2011 and May 2013. Patients were grouped by oncologic treatment: surgery (SURG; n=29), IMRT (IMRT; n=26) or IMRT combined with chemotherapy (CHIMRT; n=27). Dental screening data, demographic data, subgingival biofilm samples, oral lavages and whole saliva samples were obtained to microbiologically analyze the effects of cancer treatments (1 year follow-up). In the IMRT- and CHIMRT- group increased prevalence of enteric rods, staphylococci and *Candida* species was observed. In these groups, elimination of oral foci decreased the frequency of detection of pathogens such as *P. gingivalis*, *T. forsythia* and *S. mutans*. In the SURG group, the increase of opportunistic pathogens was not seen. The prevalence of periodontal bacterial species in SURG patients tended to decrease at 6 and 12 months, but was only statistically significant for *T. forsythia*. Thus, different treatments in HNC patients resulted in different changes in the oral microflora. Opportunistic pathogens such as staphylococci, enteric rods and *Candida* species tended to increase in prevalence after IMRT with or without chemotherapy, but not after surgical intervention.

The prospective study described in **Chapter 5** assessed the efficacy of pre-radiation dental screening and elimination of oral foci of infection to reduce post-IMRT oral sequelae. All consecutive dentate patients >18 years, diagnosed with a primary oral or oropharynx carcinoma, seen for pre-treatment dental screening between May 2011 and May 2013, were included and followed for 2 years. Patients were subjected to IMRT or IMRT with chemotherapy (CHIMRT). Dental screening data, demographic data and data on oral sequelae during follow-up were recorded. Oral foci were found in 44/56 (79%) patients and consisted predominantly of periodontal breakdown. Bone healing problems after radiotherapy occurred more often in patients with periodontal pockets ≥6 mm at baseline ($p<0.05$). Osteoradionecrosis developed in 4/56 patients (7%) during follow-up. It was concluded that patients with periodontal disease before radiotherapy are prone to develop bone healing problems after IMRT/CHIMRT.

The prospective study described in **Chapter 6** assessed the effect of leaving chronic oral foci of infection untreated on the development of infectious complications in intensively treated hematological patients. Included were 28 intensively treated leukemic patients and 35 patients undergoing high-dose chemotherapy and autologous stem cell transplantation (ASCT), between September 2012 and May 2014. Acute oral foci of infection (tooth related or oral mucosa related pain, percussion or palpation tenderness of oral structures, fever related to oral pathology, swelling of oral tissues and/or tooth related purulent drainage) were removed before chemotherapy or ASCT, while chronic oral foci (focus had not exacerbated and was asymptomatic during the previous 3 months) were left untreated. Acute oral foci of infection were found in 2 leukemic (7%) and 2 ASCT-patients (6%), chronic oral foci of infection in 24 leukemic (86%) and 22 ASCT-patients (63%). Positive blood cultures with microorganisms potentially originating from the oral cavity occurred in 7 patients during treatment, but were uneventful on development of infectious complications. The results of this prospective study support the hypothesis that chronic oral foci of infection can be left untreated as this does not increase infectious complications during intensive chemotherapy.

In **chapter 7** the various outcomes of the studies described in the previous chapters were placed in a broader perspective. The main conclusions of the research described in this thesis are that the assessed dental screening protocol was equally effective in patients treated with conventional radiotherapy, IMRT or IMRT combined with chemotherapy (CHIMRT) as the post-radiotherapy oral and dental morbidity was comparable. Not all oral sequelae can be prevented, however, and thus the need for further research remains. Also, HNC patients with periodontal disease before radiotherapy were shown to be prone to develop bone healing problems after radiotherapy.

In hematology patients, it was shown that chronic oral foci of infection can be left untreated as leaving these foci untreated does not increase infectious complications during intensive chemotherapy.

Chapter 9

Samenvatting

Patiënten die vanwege een oncologische aandoening in het hoofd-halsgebied zullen worden behandeld met radiotherapie, al dan niet in combinatie met chemotherapie, ondergaan een tandheelkundig focusonderzoek. Bij dit focusonderzoek worden afwijkingen opgespoord die tijdens of na de oncologische behandeling tot problemen kunnen leiden; de zogenaamde orale foci. Er wordt bij het focusonderzoek een verschil gemaakt tussen patiënten die vanwege een tumor in het hoofd-halsgebied met radiotherapie worden behandeld en patiënten die vanwege een hematologische aandoening met hoge doses chemotherapie worden behandeld. Radiotherapie in het hoofd-hals gebied gaat namelijk gepaard met een levenslang risico op het ontwikkelen van gebits- en tandvleesproblemen (cariës, parodontitis) en slecht tot niet genezende ontstekingen van het kaakbot (osteoradionecrose). Dit is het gevolg van onherstelbare bestralingsschade aan de harde en zachte weefsels in en rond de mond. Bij de behandeling van hematologische aandoeningen met hoge doses chemotherapie is de schade aan zachte en harde weefsels in en rond de mond echter van tijdelijke aard. Wat als een oraal focus moet worden beschouwd verschilt dus tussen beide patiëntengroepen. Een patiënt die chemotherapie ondergaat heeft, na herstel van de bloedwaarden, namelijk geen hoger risico op het ontwikkelen van complicaties veroorzaakt door orale foci dan een gezonde patiënt. Bij de bestraalde patiënt blijft dit hogere risico levenslang aanwezig! Hoewel het tandheelkundig focusonderzoek voor deze aandoeningen wereldwijd wordt verricht, is de effectiviteit hiervan niet in gedegen onderzoek aangetoond. Dat het tandheelkundig focusonderzoek als effectief wordt beschouwd is hoofdzakelijk gebaseerd op klinische ervaring.
Het doel van het in dit proefschrift beschreven onderzoek is te beoordelen of het tandheelkundig focusonderzoek effectief ingezet kan worden om de kans op het ontwikkelen van mondproblemen tijdens en na de behandeling van kanker te verminderen bij patiënten die worden behandeld met radiotherapie in het hoofd-halsgebied en/of met hoge doses chemotherapie bij hematologische aandoeningen.

Om de effectiviteit van het tandheelkundig focusonderzoek te beoordelen werd een systematisch literatuuronderzoek uitgevoerd (**Hoofdstuk 2**). Daartoe zijn de databases MEDLINE en EMBASE doorzocht op artikelen waarin de effectiviteit van tandheelkundig focusonderzoek is beschreven. Van de 1770 tot mei 2014 gepubliceerde artikelen voldeden 20 artikelen aan de inclusiecriteria. Zeventien van deze 20 artikelen beschreven de resultaten van retrospectieve studies. De heterogeniteit van de in deze studies beschreven patiëntgroepen was groot, net als hoe het focusonderzoek was uitgevoerd. Ook verschilde tussen de studies wat als een oraal focus werd beschouwd en hoe een oraal focus werd behandeld. Op basis van deze bevindingen kon worden geconcludeerd dat het beschikbare bewijs over de effectiviteit van het preradiotherapeutische focusonderzoek van onvoldoende kwaliteit bleek om duidelijkheid te verschaffen over de effectiviteit van het focusonderzoek.

In **hoofdstuk 3** wordt een studie beschreven waarin retrospectief werd geëvalueerd of het preradiotherapeutische focusonderzoek effectief was en, in het bijzonder, welke foci als risicofactoren moeten worden beschouwd voor het ontwikkelen van orale problemen na afloop van de radiotherapie. Daartoe werden de gegevens van 185 opeenvolgende hoofd-hals oncologiepatiënten die tussen januari 2004 en december 2008 een focusonderzoek in het Universitair Medisch Centrum Groningen hadden ondergaan geanalyseerd. Van deze groep van 185 patiënten konden 80 patiënten met (nog) eigen tanden en kiezen ten behoeve van deze studie worden geïncludeerd. Orale foci, vooral parodontale problemen, werden in 76% van de patiënten gevonden. Osteoradionecrose (ORN) van de boven- of onderkaak bleek zich in 9 van de 80 patiënten (11%) te hebben ontwikkeld. Vooral patiënten bij wie tijdens het focusonderzoek pockets ≥6mm werden aangetroffen, bleken een verhoogd risico te hebben op het ontwikkelen van ORN. De kans op het ontwikkelen van ORN was vooral hoog wanneer gebitselementen met pockets ≥6mm niet voorafgaand aan de radiotherapie waren geëxtraheerd, maar waren behandeld door middel van initiële parodontale therapie. Op basis van de uitkomsten van deze retrospectieve studie moesten een slechte parodontale conditie tijdens het focusonderzoek en initiële parodontale therapie in plaats van extractie als risicofactoren voor het ontwikkelen van ORN worden aangemerkt.

Het is onbekend hoe modernere behandelmodaliteiten als ‘intensity modulated radiation therapy’ (IMRT) en IMRT gecombineerd met chemotherapie (CHIMRT) de samenstelling van de orale flora beïnvloeden. De dosisverdeling in de harde en zachte weefsels in en rond de mond is door de toepassing van IMRT veranderd. IMRT beoogt bepaalde kritische weefsels, zoals speekselklieren, zoveel mogelijk te sparen, terwijl de cumulatieve dosis op het tumorweefsel zelf onveranderd blijft. Toepassing van IMRT en/of CHIMRT zou kunnen leiden tot een hoger of juist lager risico op het ontwikkelen van mondproblemen in vergelijking met conventionele bestralingstechnieken. In **hoofdstuk 4** wordt een prospectieve studie beschreven waarin de effecten van een aantal behandelmodaliteiten op de samenstelling van de orale flora zijn onderzocht. Tussen mei 2011 en mei 2013 werden 82 patiënten met een mondholte- of orofarynxcarcinoom onderworpen aan een tandheelkundig focusonderzoek. Patiënten werden aan de hand van hun oncologische behandeling gegroepeerd te weten chirurgie (SURG; n=29), IMRT (n=26) of CHIMRT (n=27). Data van het focusonderzoek, demografische data, microbiële data van subgingivale biofilms en mondspoelingen, en speekselmonsters werden geanalyseerd om de effecten van deze behandelingen op de microflora te beoordelen (1 jaar follow-up). In de IMRT- en CHIMRT-groep bleek de prevalentie van Gram-negatieve staven, stafylokokken en *Candida* soorten significant te zijn toegenomen. Eliminatie van de orale foci in deze beide groepen resulteerde in een afname van pathogene bacteriën zoals *Porphyromonas gingivalis, Tannerella forsythia* en *Streptococcus mutans.* In de SURG-groep werd geen toename van deze opportunistische pathogenen gezien. De prevalentie van paropathogenen toonde een

daling tijdens de follow-up in deze groep, maar deze daling was alleen significant voor *T. forsythia*. Met andere woorden, de veranderingen die in de samenstelling van de orale flora optreden zijn afhankelijk van de uitgevoerde kankerbehandeling.

De in **hoofdstuk 5** beschreven prospectieve studie behandelt het effect van het tandheelkundig focusonderzoek en het verwijderen van orale foci voorafgaand aan IMRT op het voorkomen van orale problemen na afloop van de IMRT. Tussen mei 2011 en mei 2013 werden 56 opeenvolgende patiënten met een tumor in het hoofd-halsgebied gezien voor een tandheelkundig focusonderzoek in het Universitair Medisch Centrum Groningen. Vervolgens werden zij behandeld met curatieve IMRT of CHIMRT en gedurende 2 jaar gevolgd. Orale foci, opnieuw voornamelijk parodontale problemen, werden in 79% van de patiënten gevonden. Problemen met de botgenezing na IMRT/CHIMRT werden, in overeenstemming met de in hoofdstuk 3 beschreven studie, vaker gezien bij patiënten met pockets ≥6mm ten tijde van het focusonderzoek ($p<0.05$). ORN ontwikkelde zich in 7% van deze patiënten. Met andere woorden, patiënten met parodontitis vóór aanvang van de radiotherapie hebben meer kans op het ontwikkelen van botgenezingsproblemen na IMRT/CHIMRT.

De in **hoofdstuk 6** beschreven prospectieve studie beschrijft het effect van het onbehandeld laten van chronische orale foci op het ontwikkelen van infectieuze complicaties bij hematologie patiënten die werden behandeld met hoge doses chemotherapie. Tussen september 2012 en mei 2014 werden 28 leukemiepatiënten die intensieve chemotherapie ondergingen en 35 patiënten die werden behandeld met hoge doses chemotherapie en autologe stamceltransplantatie (ASCT) geïncludeerd. Voorafgaand aan de chemotherapie of ASCT werden acute orale foci verwijderd (foci met symptomen orale pijn, zwelling van orale weefsels, pusafvloed gerelateerd aan gebitselementen), terwijl chronische orale foci (foci zonder symptomen in de afgelopen 3 maanden) onbehandeld bleven. Acute orale foci werden in 2 leukemie (7%) en 2 ASCT-patiënten (6%) gezien, chronische orale foci in 24 leukemie (86%) en 22 ASCT-patiënten (63%). Positieve bloedkweken met micro-organismen die afkomstig zouden kunnen zijn uit de mondholte werden bij 7 patiënten gevonden. Deze positieve bloedkweken leidden echter niet tot infectieuze complicaties. De uitkomst van deze prospectieve studie steunt de hypothese dat chronische orale foci in deze patiëntengroepen niet hoeven te worden behandeld voorafgaand aan de behandeling met hoge doses chemotherapie.

In **hoofdstuk 7** worden de bevindingen uit de diverse in dit proefschrift beschreven studies in een breder perspectief gezet. De belangrijkste conclusies die uit deze studies kunnen worden getrokken zijn dat het onderzochte protocol voor het tandheelkundig focusonderzoek even effectief was bij patiënten die werden behandeld met conventionele radiotherapie, IMRT of IMRT gecombineerd met chemotherapie (CHIMRT). In het kader van wat wel of niet als een focus moet worden gezien, is de bevinding dat de kans op het optreden van botgenezingsstoornissen na radiotherapie in het hoofd-halsgebied verhoogd is in patiënten met parodontitis.
Met betrekking tot de behandeling van patiënten met een hematologische aandoening met intensieve chemotherapie en/of autologe stamceltransplantatie is aangetoond dat chronische, asymptomatische orale foci niet behandeld hoeven te worden voorafgaand aan of tijdens de oncologische behandeling van deze patiënten.

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Dankwoord

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Curriculum Vitae

Jennifer Marleen Schuurhuis was born on November 15th in Zwolle, the Netherlands. After finishing secondary school in 2003, she studied Dentistry at the University of Groningen. During her study, she did an internship at the University of the Western Cape, in Cape Town, South Africa. After graduating in 2009, she started her PhD research project at the University of Groningen and combined this with her work as general dental practitioner in Peize and later in Leek, Beilen, Erica and Zwolle. Marleen is married to Gerjohn IJzerman. Together they have a son, Sem, who was born on June 4th 2016.

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